

LAP20 Rec'd PCT/PTO 22 MAR 2006

**BENZIMIDAZOLE DERIVATIVES, COMPOSITIONS CONTAINING
THEM, PREPARATION THEREOF AND USES THEREOF**

5 **BACKGROUND OF THE INVENTION**

1. Field of the invention

The invention is related to therapeutic compounds, pharmaceutical compositions containing these compounds, manufacturing processes thereof and uses thereof. Particularly, the present invention is related to compounds that may be effective in treating pain, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and/or cardiovascular disorders.

2. Discussion of Relevant Technology

15 Pain management has been an important field of study for many years. It has been well known that cannabinoid receptor (e.g., CB₁ receptor, CB₂ receptor) ligands including agonists, antagonists and inverse agonists produce relief of pain in a variety of animal models by interacting with CB₁ and/or CB₂ receptors. Generally, CB₁ receptors are located predominately in the central nervous system, whereas CB₂ receptors are located primarily in the periphery and are primarily restricted to the cells and tissues derived from the immune system.

While CB₁ receptor agonists, such as Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and anadamide, are useful in anti-nociception models in animals, they tend to exert undesired CNS side-effects, e.g., psychoactive side effects, the abuse potential, drug dependence and tolerance, etc. These undesired side effects are known to be mediated by the CB₁ receptors located in CNS. There are lines of evidence, however, suggesting that CB₁ agonists acting at peripheral sites or with limited CNS exposure can manage pain in humans or animals with much improved overall in vivo profile.

Therefore, there is a need for new CB₁ receptor ligands such as agonists that may be useful in managing pain or treating other related symptoms or diseases with reduced or minimal undesirable CNS side-effects.

DESCRIPTION OF THE EMBODIMENTS

The present invention provides CB₁ receptor ligands which may be useful in treating pain and/or other related symptoms or diseases.

Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures.

"CB₁/CB₂ receptors" means CB₁ and/or CB₂ receptors.

The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms.

The term "hydrocarbon" used alone or as a suffix or prefix, refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms. The term "hydrocarbon radical" or "hydrocarbyl" used alone or as a suffix or prefix, refers to any structure as a result of removing one or more hydrogens from a hydrocarbon.

The term "alkyl" used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms. Unless otherwise specified, "alkyl" general includes both saturated alkyl and unsaturated alkyl.

The term "alkylene" used alone or as a suffix or prefix, refers to divalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms, which serves to links two structures together.

The term "alkenyl" used alone or as a suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 2 up to about 12 carbon atoms.

The term "alkynyl" used alone or as a suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond and comprising at least 2 up to about 12 carbon atoms.

The term "cycloalkyl," used alone or as a suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms. "Cycloalkyl" includes both monocyclic and multicyclic hydrocarbon

structures. Multicyclic hydrocarbon structure includes non-fused, fused and bridged rings.

The term "cycloalkenyl" used alone or as a suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms. "Cycloalkenyl" includes both monocyclic and multicyclic hydrocarbon structures. Multicyclic hydrocarbon structure includes non-fused, fused and bridged rings.

The term "cycloalkynyl" used alone or as a suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon triple bond and comprising about 7 up to about 12 carbon atoms. "Cycloalkenyl" includes both monocyclic and multicyclic hydrocarbon structures. Multicyclic hydrocarbon structure includes non-fused, fused and bridged rings.

The term "aryl" used alone or as a suffix or prefix, refers to a hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, $4n + 2$ delocalized electrons) and comprising 5 up to about 14 carbon atoms, wherein the radical is located on a carbon of the aromatic ring.

The term "non-aromatic group" or "non-aromatic" used alone, as a suffix or as prefix, refers to a chemical group or radical that does not contain a ring having aromatic character (*e.g.*, $4n + 2$ delocalized electrons).

The term "arylene" used alone or as a suffix or prefix, refers to a divalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, $4n + 2$ delocalized electrons) and comprising 5 up to about 14 carbon atoms, which serves to link two structures together.

The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

The term "heteroalkyl" used alone or as a suffix or prefix, refers to a radical formed as a result of replacing one or more carbon atom of an alkyl with one or more heteroatoms selected from N, O, P and S.

5 The term "heteroaromatic" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-containing structure or molecule has an aromatic character (*e.g.*, $4n + 2$ delocalized electrons).

10 The term "heterocyclic group," "heterocyclic moiety," "heterocyclic," or "heterocyclo" used alone or as a suffix or prefix, refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

15 The term "heterocyclyl" used alone or as a suffix or prefix, refers a radical derived from a heterocycle by removing at least one hydrogen from a carbon of a ring of the heterocycle.

The term "heterocyclylene" used alone or as a suffix or prefix, refers to a divalent radical derived from a heterocycle by removing two hydrogens therefrom, which serves to links two structures together.

20 The term "heteroaryl" used alone or as a suffix or prefix, refers to a heterocyclyl having aromatic character, wherein the radical of the heterocyclyl is located on a carbon of an aromatic ring of the heterocyclyl. A heteroaryl may contain both aromatic and non-aromatic rings therein. These rings may be fused or otherwise linked together.

25 The term "heterocylcoalkyl" used alone or as a suffix or prefix, refers to a heterocyclyl that does not have aromatic character.

The term "heteroarylene" used alone or as a suffix or prefix, refers to a heterocyclylene having aromatic character.

The term "heterocycloalkylene" used alone or as a suffix or prefix, refers to a heterocyclylene that does not have aromatic character.

30 The term "six-membered" used as prefix refers to a group having a ring that contains six ring atoms.

The term "five-membered" used as prefix refers to a group having a ring that contains five ring atoms.

A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, 5 tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl.

A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, 10 triazinyl and pyridazinyl.

The term "substituted" used as a prefix refers to a structure, molecule or group, wherein one or more hydrogens are replaced with one or more C₁₋₁₂hydrocarbon groups, or one or more chemical groups containing one or more heteroatoms selected from N, O, S, F, Cl, Br, I, and P. Exemplary chemical groups 15 containing one or more heteroatoms include heterocyclyl, -NO₂, -OR, -Cl, -Br, -I, -F, -CF₃, -C(=O)R, -C(=O)OH, -NH₂, -SH, -NHR, -NR₂, -SR, -SO₃H, -SO₂R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR₂, -NRC(=O)R, oxo (=O), imino (=NR), thio (=S), and oximino (=N-OR), wherein each "R" is a C₁₋₁₂hydrocarbyl. For example, substituted phenyl may refer to nitrophenyl, pyridylphenyl, methoxyphenyl, 20 chlorophenyl, aminophenyl, etc., wherein the nitro, pyridyl, methoxy, chloro, and amino groups may replace any suitable hydrogen on the phenyl ring.

The term "substituted" used as a suffix of a first structure, molecule or group, followed by one or more names of chemical groups refers to a second structure, molecule or group, which is a result of replacing one or more hydrogens of the first 25 structure, molecule or group with the one or more named chemical groups. For example, a "phenyl substituted by nitro" refers to nitrophenyl.

The term "optionally substituted" refers to both groups, structures, or molecules that are substituted and those that are not substituted.

Heterocycle includes, for example, monocyclic heterocycles such as: 30 aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane, 2,3-dihydrofuran, 2,5-dihydrofuran, tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran,

tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4-oxadiazole.

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

Heterocyclyl includes, for example, monocyclic heterocyclyls, such as: aziridinyl, oxiranyl, thiiiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl,

imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4 oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including
5 both aromatic or non-aromatic), for example, indolyl, indolynyl, isoindolynyl, quinolynyl, tetrahydroquinolynyl, isoquinolynyl, tetrahydroisoquinolynyl, 1,4-benzodioxanyl, coumarinyl, dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl, xanthenyl, phenoxathiinyl, thianthrenyl, indolizynyl, isoindolyl, indazolyl, purinyl,
10 phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolynyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrolizidinyl, and quinolizidinyl.

15 In addition to the polycyclic heterocyclyls described above, heterocyclyl includes polycyclic heterocyclyls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocyclyls include quinuclidinyl, diazabicyclo[2.2.1]heptyl; and 7-oxabicyclo[2.2.1]heptyl.

20 The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula -O-R, wherein -R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

The term "aryloxy" used alone or as a suffix or prefix, refers to radicals of the
25 general formula -O-Ar, wherein -Ar is an aryl.

The term "heteroaryloxy" used alone or as a suffix or prefix, refers to radicals of the general formula -O-Ar', wherein -Ar' is a heteroaryl.

The term "amine" or "amino" used alone or as a suffix or prefix, refers to radicals of the general formula -NRR', wherein R and R' are independently selected
30 from hydrogen or a hydrocarbon radical.

"Acyl" used alone, as a prefix or suffix, means -C(=O)-R, wherein -R is an optionally substituted hydrocarbyl, hydrogen, amino or alkoxy. Acyl groups include,

for example, acetyl, propionyl, benzoyl, phenyl acetyl, carboethoxy, and dimethylcarbamoyl.

Halogen includes fluorine, chlorine, bromine and iodine.

"Halogenated," used as a prefix of a group, means one or more hydrogens on the group is replaced with one or more halogens.

"RT" or "rt" means room temperature.

A first ring group being "fused" with a second ring group means the first ring and the second ring share at least two atoms therebetween.

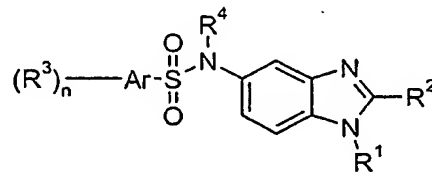
"Link," "linked," or "linking," unless otherwise specified, means covalently linked or bonded.

When a first group, structure, or atom is "directly connected" to a second group, structure or atom, at least one atom of the first group, structure or atom forms a chemical bond with at least one atom of the second group, structure or atom.

"Saturated carbon" means a carbon atom in a structure, molecule or group wherein all the bonds connected to this carbon atom are single bond. In other words, there is no double or triple bonds connected to this carbon atom and this carbon atom generally adopts an sp^3 atomic orbital hybridization.

"Unsaturated carbon" means a carbon atom in a structure, molecule or group wherein at least one bond connected to this carbon atom is not a single bond. In other words, there is at least one double or triple bond connected to this carbon atom and this carbon atom generally adopts a sp or sp^2 atomic orbital hybridization.

In one aspect, an embodiment of the invention provides a compound of Formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:

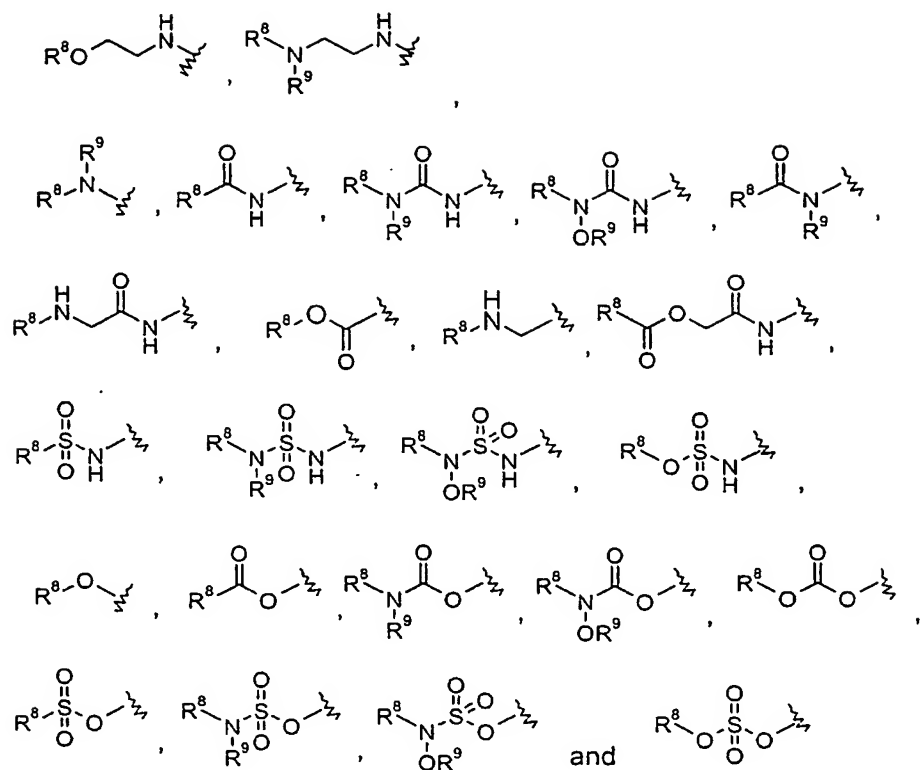


I

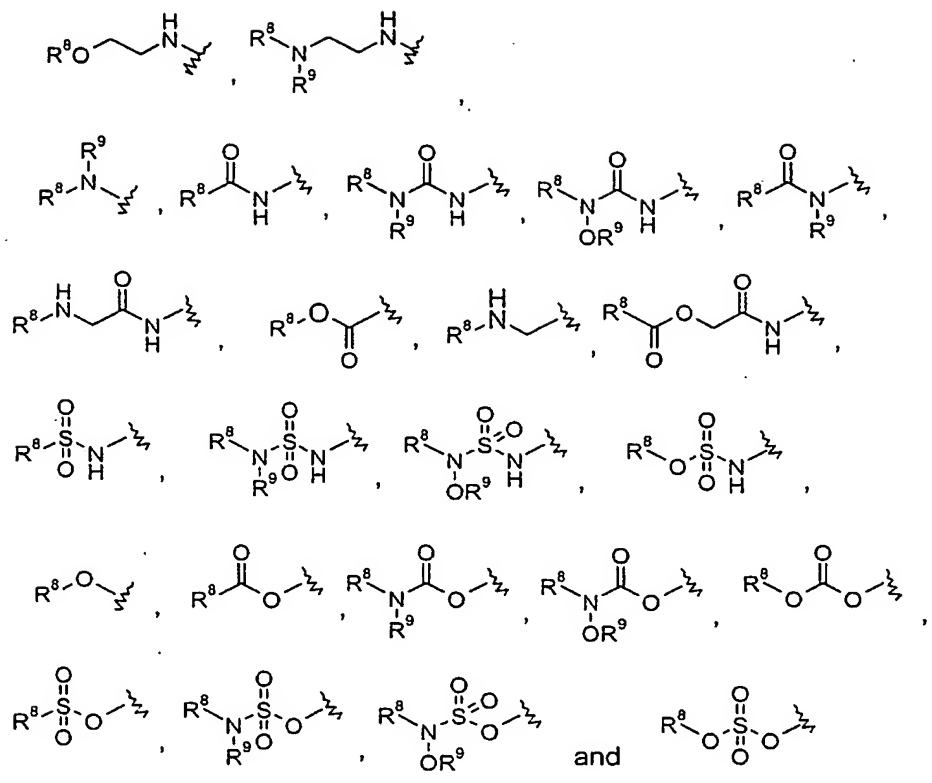
wherein

R^1 is selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $R^5-C(=O)-O-$, C_{1-6} alkyl, $R^5R^6N-C_{1-6}$ alkyl, R^5O-C_{1-6} alkyl, $R^5C(=O)N(-R^6)-C_{1-6}$ alkyl, $R^5R^6NS(=O)_2-$

- C_{1-6} alkyl, $R^5CS(=O)_2N(-R^6)-C_{1-6}$ alkyl, $R^5R^6NC(=O)N(-R^7)-C_{1-6}$ alkyl,
 $R^5R^6NS(=O)_2N(R^7)-C_{1-6}$ alkyl, C_{6-10} aryl- C_{1-6} alkyl, C_{6-10} aryl- $C(=O)-C_{1-6}$ alkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-6}$ alkyl, C_{1-10} hydrocarbylamino, R^5R^6N- , R^5O- , $R^5C(=O)N(-R^6)-$, $R^5R^6NS(=O)_2-$, $R^5CS(=O)_2N(-R^6)-$, $R^5R^6NC(=O)N(-R^7)-$, $R^5R^6NS(=O)_2N(R^7)-$,
 C_{6-10} aryl, C_{6-10} aryl- $C(=O)-$, C_{3-10} cycloalkyl, C_{4-8} cycloalkenyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl- $C(=O)-$; wherein said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{6-10} aryl- C_{1-6} alkyl, C_{6-10} aryl- $C(=O)-C_{1-6}$ alkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-6}$ alkyl, C_{1-10} hydrocarbylamino, C_{6-10} aryl, C_{6-10} aryl- $C(=O)-$, C_{3-10} cycloalkyl, C_{4-8} cycloalkenyl, C_{3-6} heterocyclyl or C_{3-6} heterocyclyl- $C(=O)-$ used in defining R^1 is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, benzyl, and $-NR^5R^6$;
 R^2 is selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl, R^5R^6N- , C_{3-5} heteroaryl, C_{6-10} aryl and C_{3-6} heterocycloalkyl, wherein said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl, C_{3-5} heteroaryl, C_{6-10} aryl or C_{3-6} heterocycloalkyl used in defining R^2 is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$;
 wherein R^5 , R^6 and R^7 are independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a divalent C_{1-6} group that together with another divalent R^5 , R^6 or R^7 forms a portion of a ring;
 Ar is selected from C_{6-10} aryl and C_{3-8} heteroaryl;
 n is selected from 0, 1, 2 and 3;
 each of R^3 is independently selected from $-H$, nitro, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocycloalkyl- C_{1-6} alkyl, C_{3-6} heterocycloalkyl,



optionally substituted with one or more groups selected from C₁₋₆alkyl, hydroxy, halogen, amino and C₁₋₆alkoxy,



- each of R^8 and R^9 is independently selected from $-H$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl, C_{6-10} aryl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{6-10} aryl- C_{1-6} alkyl, and a divalent C_{1-6} group that together with another divalent group selected from R^8 and R^9 forms a portion of a ring, wherein said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl, C_{6-10} aryl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{6-10} aryl- C_{1-6} alkyl, or divalent C_{1-6} group is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$; and
- R^4 is selected from $-H$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, and C_{4-8} cycloalkenyl- C_{1-6} alkyl.

- Another embodiment of the invention provides a compound of Formula I, wherein
- R^1 is selected from C_{1-6} alkyl, C_{1-6} alkyl- $C(=O)-O-C_{1-4}$ alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl- C_{1-4} alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_3 .

6heterocyclyl-C₁₋₄alkyl, C₆₋₁₀aryl, C₃₋₆heterocyclyl, C₃₋₁₀cycloalkyl, and C₄₋₆cycloalkenyl, wherein said C₁₋₆alkyl, C₁₋₆alkyl-C(=O)-O-C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, phenyl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl-C₁₋₄alkyl, C₄₋₆cycloalkenyl-C₁₋₄alkyl, C₆₋₁₀aryl, C₃₋₆heterocyclyl-C₁₋₄alkyl, C₃₋₆heterocyclyl, C₃₋₁₀cycloalkyl, and C₄₋

5 cycloalkenyl used in defining R¹ is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, benzyl, and -NR⁵R⁶;

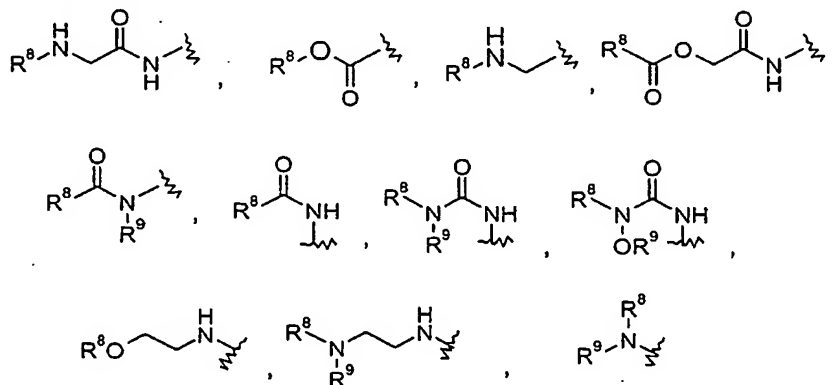
R^2 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl, C_{3-5} heteroaryl, R^5R^6N -, and phenyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl, C_{3-5} heteroaryl, R^5R^6N -, and phenyl used in defining R^2 is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and amino;

15 wherein R⁵ and R⁶ are independently selected from -H, C₁₋₆alkyl, C₂₋₆alkenyl, and a divalent C₁₋₆alkylene that together with another divalent R⁵ or R⁶ and optionally a heteroatom forms a portion of a ring;

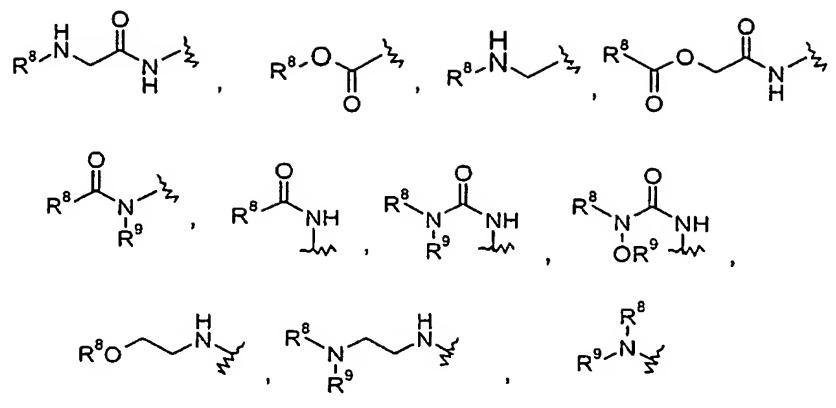
Ar is selected from phenyl and C₃₋₅heteroaryl;

n is selected from 0, 1 and 2;

20 each of R³ is independently selected from -H, nitro, halogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, C₃₋₆heterocycloalkyl-C₁₋₄alkyl,



and, C₃₋₆heterocycloalkyl optionally substituted with one or more groups selected from C₁₋₆alkyl, hydroxy, halogen and



- each of R^8 and R^9 is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl- C_{1-6} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl- C_{1-6} alkyl are optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and $-NR^{10}R^{11}$; and

R^4 , R^{10} and R^{11} are independently selected from $-H$ and C_{1-3} alkyl.

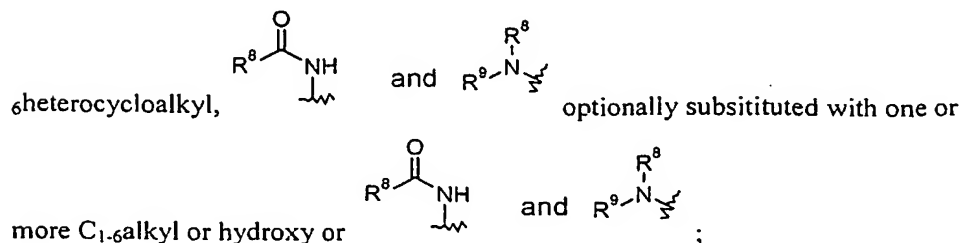
- A further embodiment of the invention provides a compound of Formula I, wherein R^1 is selected from C_{1-6} alkyl, C_{1-3} alkyl- $C(=O)-O-C_{1-3}$ alkyl, C_{2-6} alkenyl, phenyl- C_{1-4} alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, and C_{4-6} cycloalkenyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, phenyl- C_{1-4} alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, and C_{4-6} cycloalkenyl used in defining R^1 is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy, benzyl, and amino;

- R^2 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkyl- C_{1-4} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkyl- C_{1-4} alkyl used in defining R^2 is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy and amino;

Ar is selected from phenyl and C_{3-5} heteroaryl and

n is selected from 0, 1 and 2;

each of R^3 is independently selected from -H, halogen, nitro, C_{1-3} alkyl, C_{3-6} heterocycloalkyl,



wherein said C_{3-6} heterocycloalkyl contain at least one nitrogen ring atom and the radical of C_{3-6} heterocycloalkyl is located on at least one nitrogen ring atom, and wherein each of R^8 and R^9 is independently selected from -H, C_{1-6} alkyl, morpholinyl- C_{1-3} alkyl, pyrrolidinyl- C_{1-3} alkyl, and piperidinyl- C_{1-3} alkyl, wherein said C_{1-6} alkyl, morpholinyl- C_{1-3} alkyl, pyrrolidinyl- C_{1-3} alkyl, and piperidinyl- C_{1-3} alkyl are optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy and $-\text{NR}^5\text{R}^6$; and

R^4 , R^5 and R^6 are independently selected from -H and C_{1-3} alkyl.

An even further embodiment of the invention provides a compound of Formula I, wherein

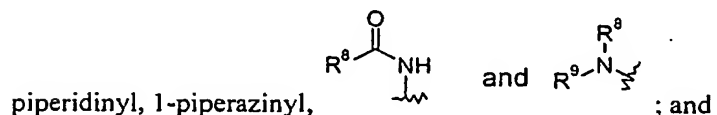
R^1 is selected from cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl, cyclohexylethyl, cyclopentylethyl, bicyclo[2.2.1]hept-5-en-2-ylmethyl, 4,4-difluorocyclohexylmethyl, tetrahydropyranylmethyl, tetrahydropyranylethyl, tetrahydrofuranylmethyl, 1-piperidinylethyl, and N-methyl-2-piperidinylmethyl;

R^2 is selected from t-butyl, n-butyl, 2-methyl-2-butyl, isopentyl, 2-methoxy-2-propyl, 2-hydroxyl-propyl, trifluoromethyl, 1,1-difluoroethyl, 2,2,2-trifluoroethyl, 1-methyl-propyl, 1,1-dimethyl-propyl, 1,1-dimethyl-3-buten-1-yl, ethyl, and 2-propyl;

Ar is selected from phenyl, pyridyl, pyrimidyl, thiazolyl, thienyl, isoxazolyl, imidazolyl, and pyrazolyl;

n is selected from 0, 1 and 2;

each of R^3 is independently selected from -H, C_{1-3} alkyl, 4-morpholinyl, 1-



piperidinyl, 1-piperazinyl,

wherein 4-morpholinyl, 1-piperidinyl, and 1-piperazinyl are optionally substituted with one or more methyl; and wherein

each of R⁸ and R⁹ is independently selected from -H, C₁₋₃alkyl, morpholinylmethyl, pyrrolidinyl-methyl, and piperidinyl-methyl, wherein said
5 C₁₋₃alkyl, morpholinylmethyl, pyrrolidinyl-methyl, and piperidinyl-methyl are optionally substituted by one or more groups selected from hydroxy, amino and dimethylamino.

It will be understood that when compounds of the present invention contain
10 one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic
15 separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of Formula I. It will
20 further be understood that the present invention encompasses tautomers of the compounds of the Formula I.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the
25 compounds of the Formula I.

Within the scope of the invention are also salts of the compounds of the Formula I. Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a
30 suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a

carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

5 In one embodiment, the compound of Formula I above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

10 We have now found that the compounds of the invention have activity as pharmaceuticals, in particular as modulators or ligands such as agonists, partial agonists, inverse agonist or antagonists of CB₁ receptors. More particularly, the compounds of the invention exhibit selective activity as agonist of the CB₁ receptors and are useful in therapy, especially for relief of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid
15 arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive. Additionally, compounds of the present invention are useful in other disease states in which dysfunction of CB₁ receptors is present or implicated. Furthermore, the compounds of the invention may be used to treat cancer, multiple sclerosis, Parkinson's disease, cancer, Huntington's chorea, Alzheimer's disease,
20 anxiety disorders, gastrointestinal disorders and cardiovascular disorders.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

25 Compounds of the invention are useful in disease states where degeneration or dysfunction of cannabinoid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

30 Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety and stress-related disorders such as post-traumatic stress disorders, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, urinary incontinence, premature ejaculation, various mental

illnesses, cough, lung oedema, various gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, Parkinson's disease and other motor disorders, traumatic brain injury, stroke, cardioprotection following myocardial infarction, spinal injury and drug
5 addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain
10 the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the Formula I above, for the manufacture of a medicament for the
15 treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I above, is administered to a patient in need of such treatment.

20 Thus, the invention provides a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

25 In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be construed accordingly. The term "therapy" within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate
30 either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound
5 of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracically, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be oral,
10 intravenous or intramuscular.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

15 For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents,
20 flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in
25 suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized moulds and allowed to cool and solidify.

30 Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

5 Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

 Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid
10 compositions can also be formulated in solution in aqueous polyethylene glycol solution.

 Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by
15 dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

 Depending on the mode of administration, the pharmaceutical composition
20 will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

 A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and
25 response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

 Within the scope of the invention is the use of any compound of Formula I as defined above for the manufacture of a medicament.

 Also within the scope of the invention is the use of any compound of Formula
30 I for the manufacture of a medicament for the therapy of pain.

 Additionally provided is the use of any compound according to Formula I for the manufacture of a medicament for the therapy of various pain conditions including,

but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a
 5 compound according to the Formula I above, is administered to a patient in need of such therapy.

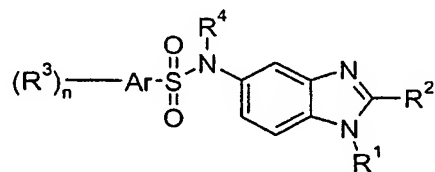
Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

10 Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

Further, there is provided a pharmaceutical composition comprising a
 15 compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

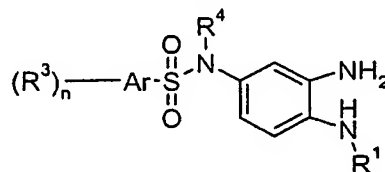
In a further aspect, the present invention provides a method of preparing the compounds of the present invention.

20 In one embodiment, the invention provides a process for preparing a compound of Formula I,



I

comprising the step of reacting a compound of Formula II,



II

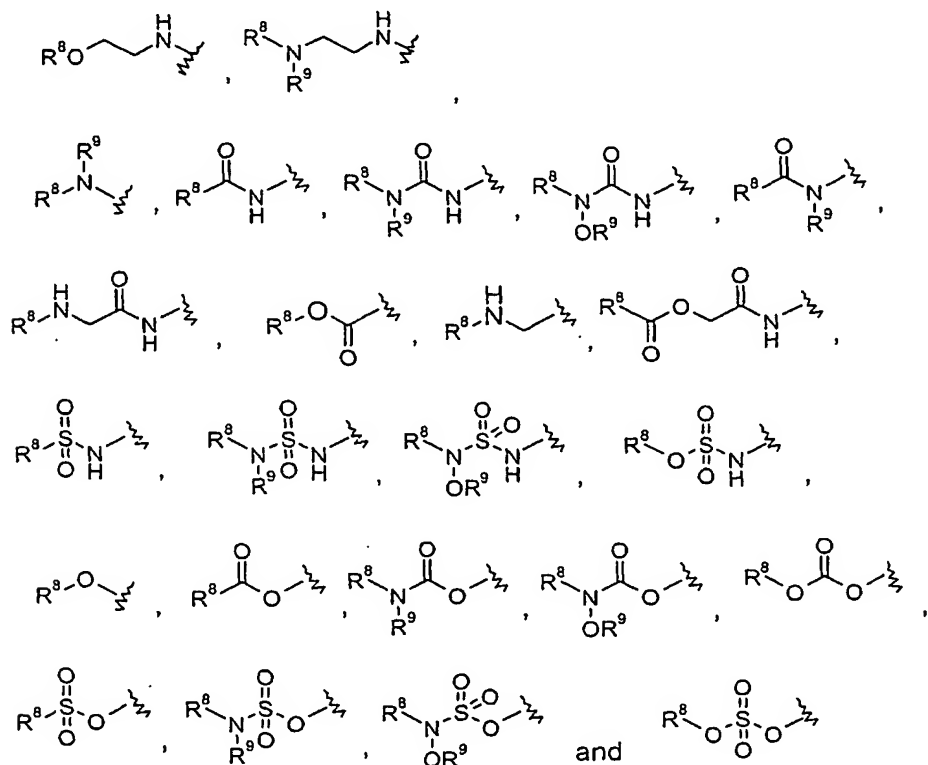
25

with a compound of R^2COX , in the presence of a base, such as an alkylamine, and optionally a coupling reagent, such as HATU, EDC, followed by treatment with an acid, such as HCl, acetic acid

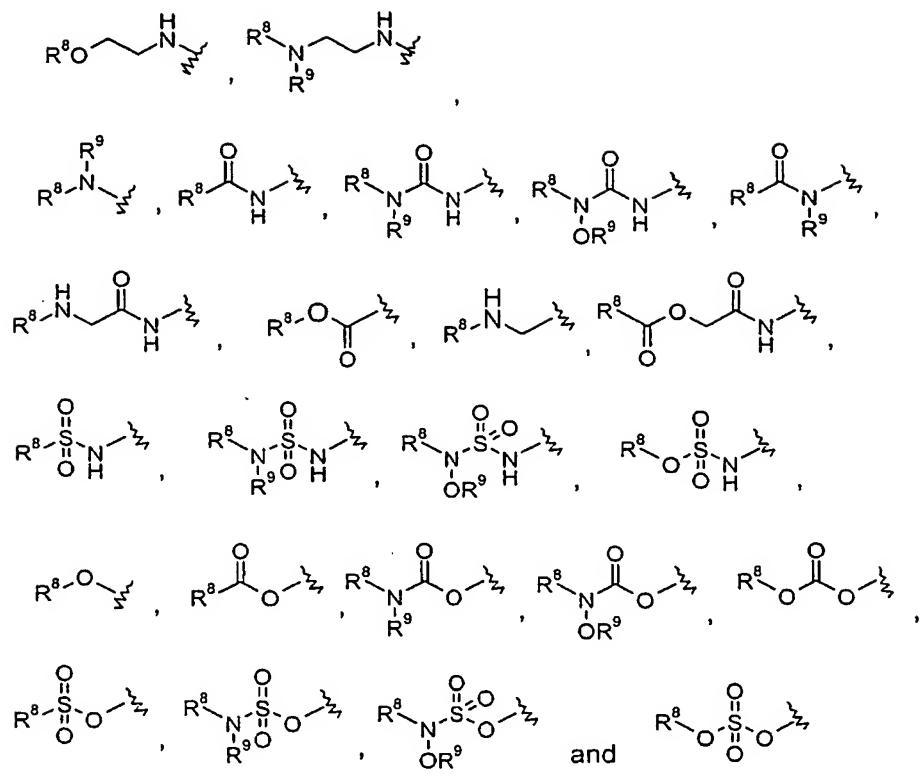
wherein

- 5 X is selected from Cl, Br, F and OH;
 R^1 is selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $R^5-C(=O)-O-$
 C_{1-6} alkyl, $R^5R^6N-C_{1-6}$ alkyl, R^5O-C_{1-6} alkyl, $R^5C(=O)N(-R^6)-C_{1-6}$ alkyl, $R^5R^6NS(=O)_2-$
 C_{1-6} alkyl, $R^5CS(=O)_2N(-R^6)-C_{1-6}$ alkyl, $R^5R^6NC(=O)N(-R^7)-C_{1-6}$ alkyl,
 $R^5R^6NS(=O)_2N(R^7)-C_{1-6}$ alkyl, C_{6-10} aryl- C_{1-6} alkyl, C_{6-10} aryl- $C(=O)-C_{1-6}$ alkyl, C_{3-}
10 $_{10}$ cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{3-}
 $_{6}$ heterocyclyl- $C(=O)-C_{1-6}$ alkyl, C_{1-10} hydrocarbylamino, R^5R^6N- , R^5O- , $R^5C(=O)N(-$
 $R^6)-$, $R^5R^6NS(=O)_2-$, $R^5CS(=O)_2N(-R^6)-$, $R^5R^6NC(=O)N(-R^7)-$, $R^5R^6NS(=O)_2N(R^7)-$,
 C_{6-10} aryl, C_{6-10} aryl- $C(=O)-$, C_{3-10} cycloalkyl, C_{4-8} cycloalkenyl, C_{3-6} heterocyclyl and C_{3-}
 $_{6}$ heterocyclyl- $C(=O)-$; wherein said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{6-10} aryl-
15 C_{1-6} alkyl, C_{6-10} aryl- $C(=O)-C_{1-6}$ alkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl-
 C_{1-6} alkyl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-6}$ alkyl, C_{1-}
 $_{10}$ hydrocarbylamino, C_{6-10} aryl, C_{6-10} aryl- $C(=O)-$, C_{3-10} cycloalkyl, C_{4-8} cycloalkenyl, C_{3-}
 $_{6}$ heterocyclyl or C_{3-6} heterocyclyl- $C(=O)-$ used in defining R^1 is optionally substituted
20 by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl,
ethyl, hydroxy, benzyl, and $-NR^5R^6$;
 R^2 is selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-}
 $_{10}$ cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocycloalkyl- C_{1-6} alkyl, C_{4-}
 $_{8}$ cycloalkenyl, R^5R^6N- , C_{3-5} heteroaryl, C_{6-10} aryl and C_{3-6} heterocycloalkyl, wherein
said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-6} alkyl,
25 C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl, C_{3-}
 $_{5}$ heteroaryl, C_{6-10} aryl or C_{3-6} heterocycloalkyl used in defining R^2 is optionally
substituted by one or more groups selected from halogen, cyano, nitro, methoxy,
ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$;
wherein R^5 , R^6 and R^7 are independently selected from $-H$, C_{1-6} alkyl, C_{2-}
30 $_{6}$ alkenyl, C_{2-6} alkynyl, and a divalent C_{1-6} group that together with another divalent R^5 ,
 R^6 or R^7 forms a portion of a ring;
Ar is selected from C_{6-10} aryl and C_{3-8} heteroaryl;
n is selected from 0, 1, 2 and 3;

each of R^3 is independently selected from -H, nitro, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocycloalkyl- C_{1-6} alkyl, C_{3-6} heterocycloalkyl and



- 5 optionally substituted with one or more groups selected from C_{1-6} alkyl, hydroxy, halogen, amino, C_{1-6} alkoxy,



- each of R^8 and R^9 is independently selected from $-H$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl, C_{6-10} aryl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{6-10} aryl- C_{1-6} alkyl, and a divalent C_{1-6} group that together with another divalent group selected from R^8 and R^9 forms a portion of a ring, wherein said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl, C_{6-10} aryl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{6-10} aryl- C_{1-6} alkyl, or divalent C_{1-6} group is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$; and
- R^4 is selected from $-H$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, and C_{4-8} cycloalkenyl- C_{1-6} alkyl.

The present invention also provides a method of preparing a compound of Formula I,

- X is selected from Cl, Br, F and OH;

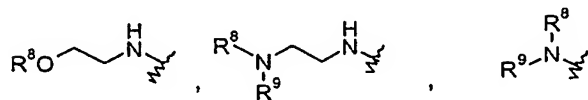
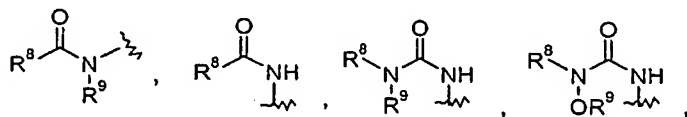
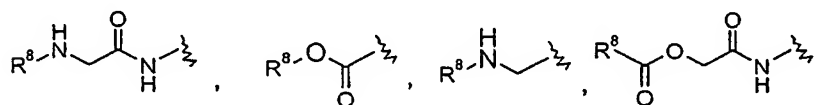
R^1 is selected from C_{1-6} alkyl, C_{1-6} alkyl- $C(=O)$ -O- C_{1-4} alkyl, C_{2-6} alkenyl, phenyl- C_{1-4} alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{6-10} aryl, C_{3-6} heterocyclyl, C_{3-6} heterocyclyl- C_{1-4} alkyl, C_{3-10} cycloalkyl, and C_{4-6} cycloalkenyl, wherein said C_{1-6} alkyl, C_{1-6} alkyl- $C(=O)$ -O- C_{1-4} alkyl, C_{2-6} alkenyl, phenyl- C_{1-4} alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{6-10} aryl, C_{3-6} heterocyclyl- C_{1-4} alkyl, C_{3-6} heterocyclyl, C_{3-10} cycloalkyl, and C_{4-6} cycloalkenyl used in defining R^1 is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy, benzyl, and amino;

R^2 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkyl- C_{1-4} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkyl- C_{1-4} alkyl used in defining R^2 is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy and amino;

Ar is selected from phenyl and C_{3-5} heteroaryl and

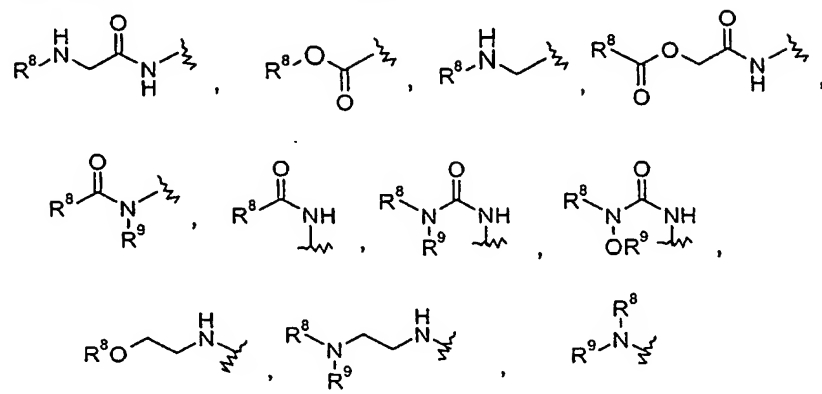
n is selected from 0, 1 and 2;

each of R^3 is independently selected from -H, nitro, halogen, C_{1-3} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl,



optionally

substituted with one or more C₁₋₆alkyl, hydroxy, halogen, and



wherein said C₃₋₆heterocycloalkyl contain at least one nitrogen ring atom and the radical of C₃₋₆heterocycloalkyl is located on the at least one nitrogen ring atom,

5 and wherein

each of R⁸ and R⁹ is independently selected from -H, C₁₋₆alkyl, morpholinyl-C₁₋₃alkyl, pyrrolidinyl-C₁₋₃alkyl, and piperidinyl-C₁₋₃alkyl, wherein said C₁₋₆alkyl, morpholinyl-C₁₋₃alkyl, pyrrolidinyl-C₁₋₃alkyl, and piperidinyl-C₁₋₃alkyl are optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy and -NR⁵R⁶; and

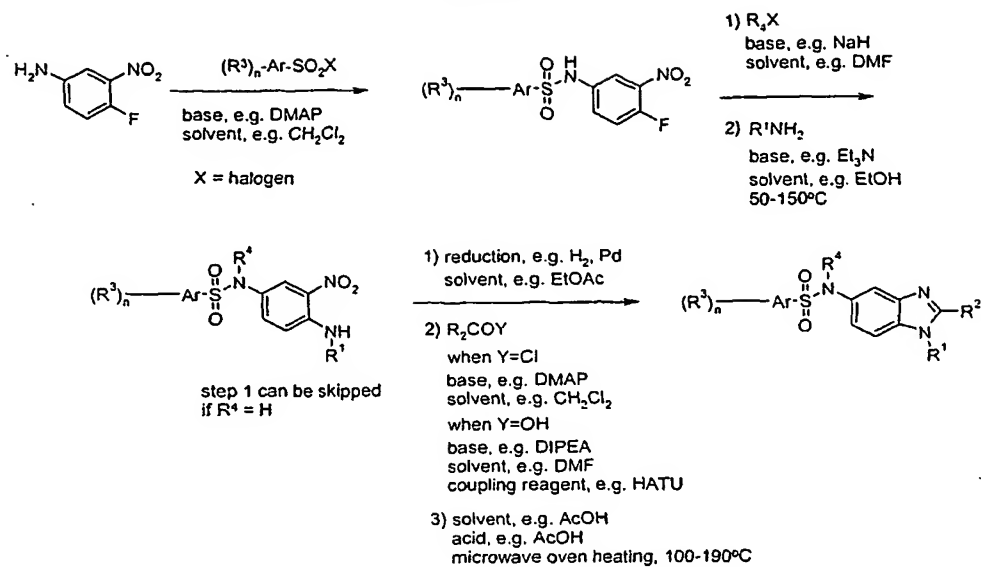
10

R⁴, R⁵ and R⁶ are independently selected from -H and C₁₋₃alkyl.

Compounds of the present invention may also be prepared according to the synthetic routes as depicted in Schemes 1-10.

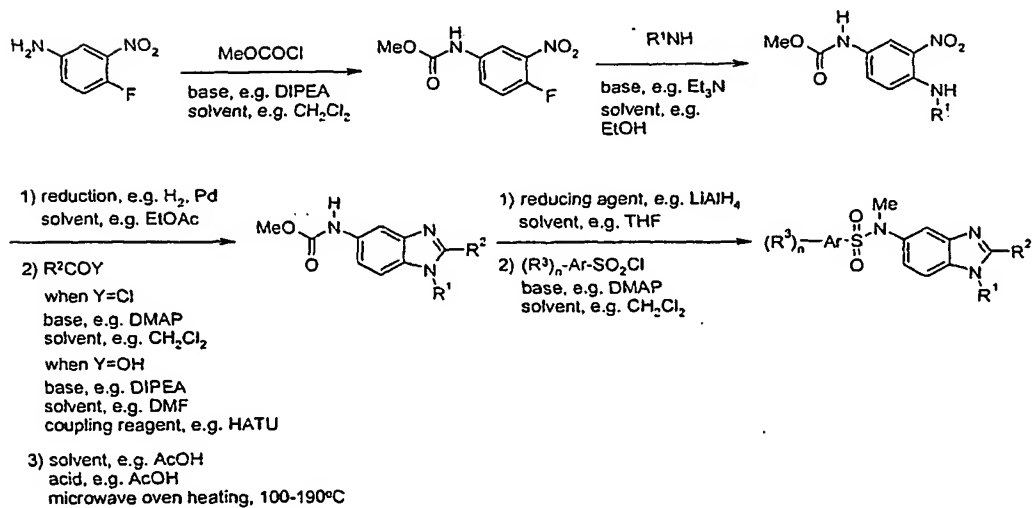
15

Scheme 1.



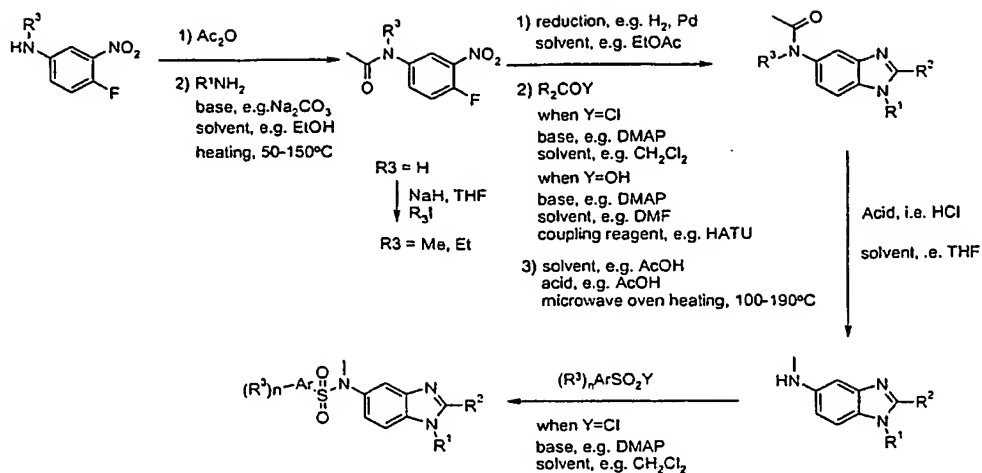
n , Ar, R^1 , R^2 , R^3 and R^4 are as defined in the specifications.

Scheme 2.



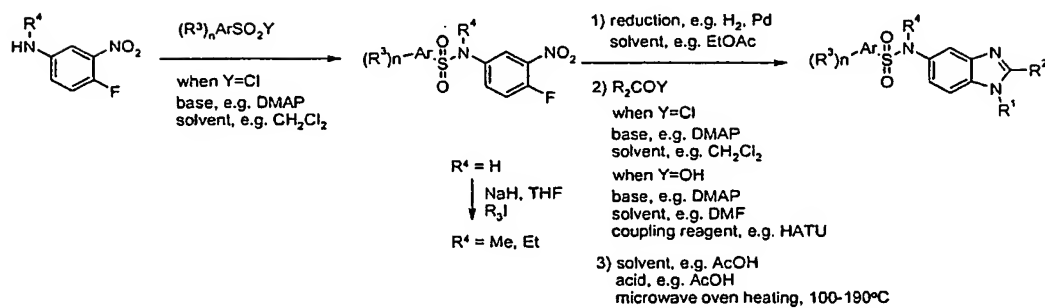
n , Ar, R^1 , R^2 and R^3 are as defined in the specifications.

Scheme 3



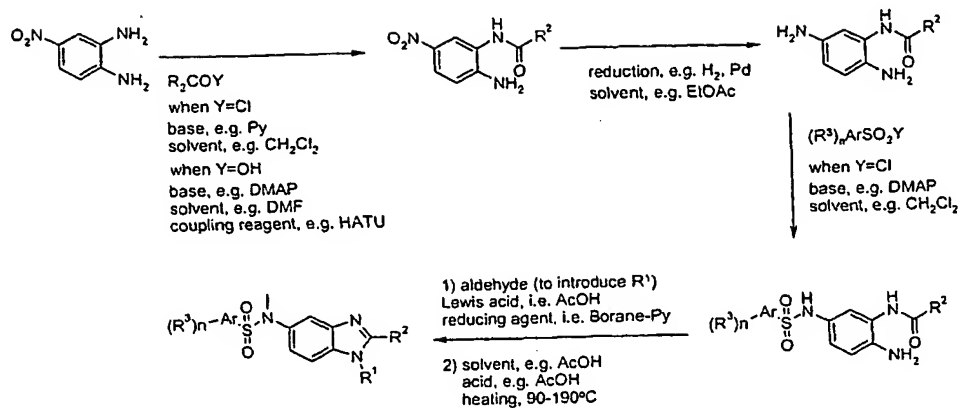
R^1 , R^2 , R^3 , and R^4 are as defined in the specifications.
 Ar is phenylene or pyridinylene.

Scheme 4



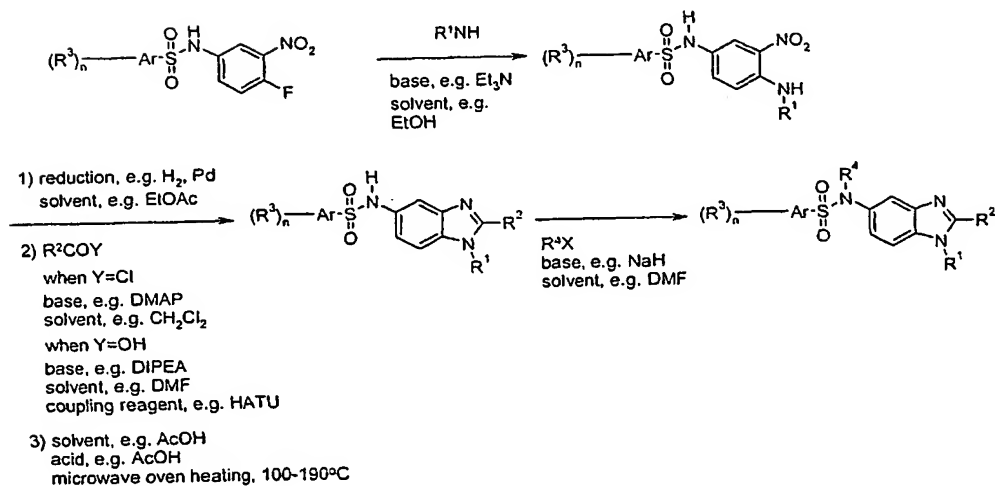
R^1 , R^2 , R^3 , and R^4 are as defined in the specifications.
 Ar is phenylene or pyridinylene.

Scheme 5



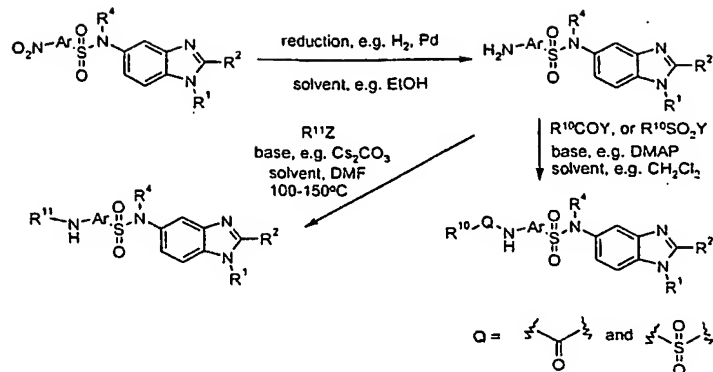
$\text{R}^1, \text{R}^2, \text{R}^3$, and R^4 are as defined in the specifications.
Ar is phenylene or pyridinylene.

Scheme 6



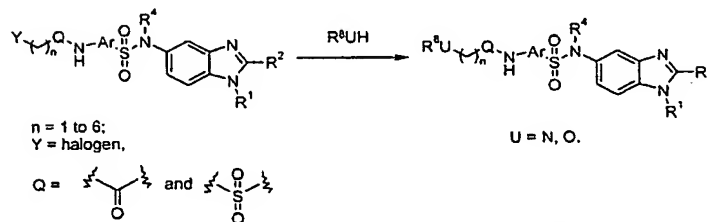
$n, \text{Ar}, \text{R}^1, \text{R}^2, \text{R}^3$ and R^4 are as defined in the specifications.

Scheme 7



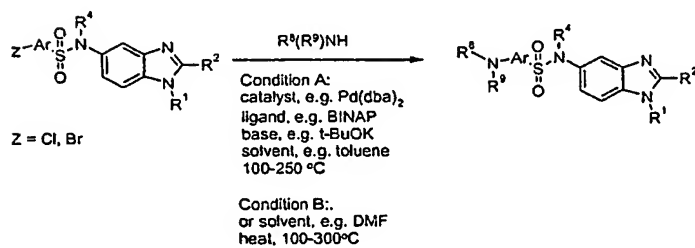
R^1 , R^2 , R^4 and Ar are as defined in the specifications;
 R^{10} and R^{11} are optionally substituted C1-6alkyl;
 Y and Z are halogen or -OH.

Scheme 8



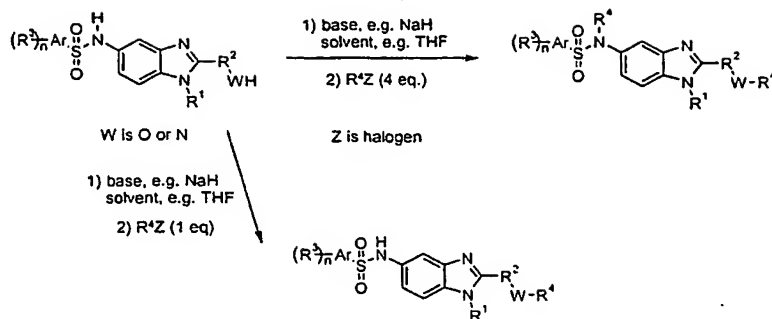
R^1 , R^2 , R^4 , R^8 and Ar are as defined in the specifications.

Scheme 9



R^1 , R^2 , R^4 , R^8 , R^9 and Ar are as defined in the specifications.

Scheme 10



R¹, R², R³, R⁴, and Ar are as defined in the specifications.

Biological Evaluation

hCB₁ and hCB₂ receptor binding

- 5 Human CB₁ receptor from Receptor Biology (hCB₁) or human CB₂ receptor from BioSignal (hCB₂) membranes are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle, diluted in the cannabinoid binding buffer (50 mM Tris, 2.5 mM EDTA, 5 mM MgCl₂, and 0.5 mg/mL BSA fatty acid free, pH 7.4) and aliquots containing the appropriate amount of protein are distributed in 96-well plates. The
- 10 IC₅₀ of the compounds of the invention at hCB₁ and hCB₂ are evaluated from 10-point dose-response curves done with ³H-CP55,940 at 20000 to 25000 dpm per well (0.17-0.21 nM) in a final volume of 300 µl. The total and non-specific binding are determined in the absence and presence of 0.2 µM of HU210 respectively. The plates are vortexed and incubated for 60 minutes at room temperature, filtered through
- 15 Unifilters GF/B (presoaked in 0.1% polyethyleneimine) with the Tomtec or Packard harvester using 3 mL of wash buffer (50 mM Tris, 5 mM MgCl₂, 0.5 mg BSA pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid.

hCB₁ and hCB₂ GTPγS binding

20 Human CB₁ receptor from Receptor Biology (hCB₁) or human CB₂ receptor membranes (BioSignal) are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle and diluted in the GTPγS binding buffer (50 mM Hepes, 20 mM NaOH, 100 mM NaCl, 1 mM EDTA, 5 mM MgCl₂, pH 7.4, 0.1% BSA). The EC₅₀

and E_{\max} of the compounds of the invention are evaluated from 10-point dose-response curves done in 300 μ l with the appropriate amount of membrane protein and 100000-130000 dpm of GTP 35 S per well (0.11 – 0.14 nM). The basal and maximal stimulated binding is determined in absence and presence of 1 μ M (hCB $_2$) or 10 μ M (hCB $_1$) Win 55,212-2 respectively. The membranes are pre-incubated for 5 minutes with 56.25 μ M (hCB $_2$) or 112.5 μ M (hCB $_1$) GDP prior to distribution in plates (15 μ M (hCB $_2$) or 30 μ M (hCB $_1$) GDP final). The plates are vortexed and incubated for 60 minutes at room temperature, filtered on Unifilters GF/B (presoaked in water) with the Tomtec or Packard harvester using 3 ml of wash buffer (50 mM Tris, 5 mM MgCl $_2$, 50 mM NaCl, pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 μ l/well of MS-20 scintillation liquid. Antagonist reversal studies are done in the same way except that (a) an agonist dose-response curve is done in the presence of a constant concentration of antagonist, or (b) an antagonist dose-response curve is done in the presence of a constant concentration of agonist.

Based on the above assays, the dissociation constant (K_i) for a particular compound of the invention towards a particular receptor is determined using the following equation:

$$K_i = IC_{50} / (1 + [rad] / K_d),$$

Wherein IC_{50} is the concentration of the compound of the invention at which 50% displacement has been observed;

[rad] is a standard or reference radioactive ligand concentration at that moment; and

K_d is the dissociation constant of the radioactive ligand towards the particular receptor.

Using the above-mentioned assays, the K_i towards human CB $_1$ receptors for most compounds of the invention is measured to be in the range of 0.7-7170 nM. The K_i towards human CB $_2$ receptors for most compounds of the invention is measured to be in the range of about 0.3-5800 nM. The EC_{50} towards human CB $_1$ receptors for most compounds of the invention is measured to be in the range of about 0.8-2810 nM. The E_{\max} towards human CB $_1$ receptors for most compounds of the invention is measured to be in the range of about 22.3-140%.

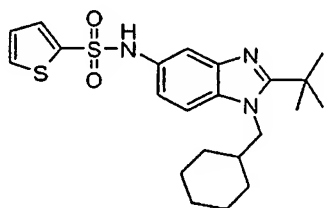
In one embodiment, the K_i towards human CB_1 receptors for most compounds of the invention is measured to be in the range of 0.7-50 nM. The K_i towards human CB_2 receptors for most compounds of the invention is measured to be in the range of about 0.3-25 nM. The EC_{50} towards human CB_1 receptors for most compounds of the invention is measured to be in the range of about 0.8-100 nM. The E_{max} towards human CB_1 receptors for most compounds of the invention is measured to be in the range of about 60-125%.

EXAMPLES

The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

Example 1

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]thiophene-2-sulfonamide



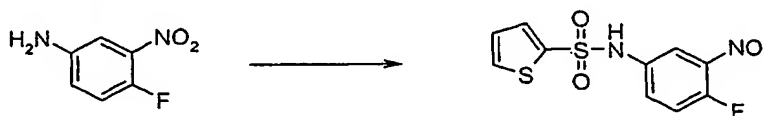
Step A. *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]thiophene-2-sulfonamide



N-[3-Amino-4-[(cyclohexylmethyl)amino]phenyl]thiophene-2-sulfonamide (55 mg, 0.150 mmol) (for preparation, see the following steps B, C and D) was dissolved in 3

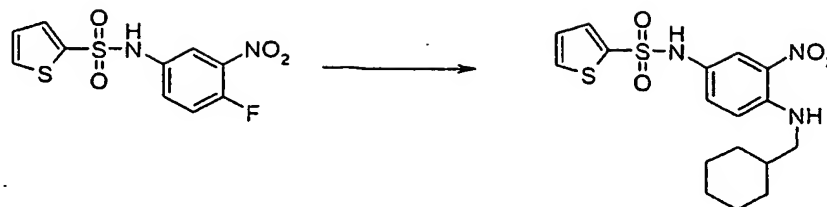
mL of 1,2-dichloroethane containing TEA (0.030 mL, 0.225 mmol). Trimethylacetyl chloride (0.020 mL, 0.165 mmol) was added dropwise and the solution was stirred at rt for 1h. Glacial AcOH (1 mL) and a few drops of concentrated HCl were added and the solution was stirred at 80°C overnight. The solvent was evaporated. The crude product was dissolved in EtOAc and washed with 2M NaOH aqueous solution, brine and dried over anhydrous MgSO₄. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 10 mg (15%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.19 (m, 5 H), 1.57 (m, 1 H), 1.59 (m, 1 H), 1.61 (s, 9 H), 1.66 (m, 1 H), 1.73 (m, 2 H), 2.05 (m, 1 H), 4.37 (d, J=7.62 Hz, 2 H), 7.02 (dd, J=4.98, 3.81 Hz, 1 H), 7.25 (dd, J=8.98, 2.15 Hz, 1 H), 7.52 (dd, J=3.71, 1.37 Hz, 1 H), 7.66 (d, J=2.15 Hz, 1 H), 7.69 (dd, J=5.08, 1.37 Hz, 1 H), 7.76 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 432.1; Anal. Calcd for C₂₂H₂₉N₃O₂S₂ + 1.4 TFA + 0.6 H₂O: C, 49.48; H, 5.29; N, 6.98. Found: C, 49.47; H, 5.36; N, 6.83.

Step B. *N*-(4-Fluoro-3-nitrophenyl)thiophene-2-sulfonamide



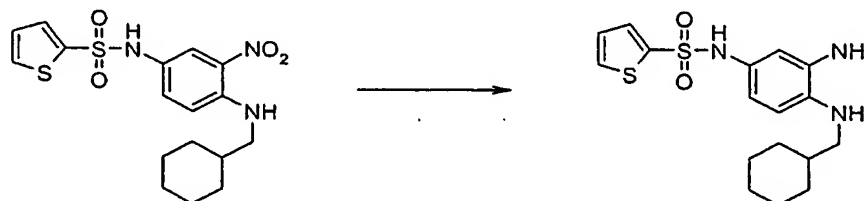
4-Fluoro-3-nitroaniline (1.00 g, 6.41 mmol) and 2-thiophenesulfonyl chloride (1.75 g, 9.62 mmol) were stirred in dichloromethane (150 mL) containing DMAP (1.17g, 9.62 mmol) at rt for 24 h. The solution was washed with 5% KHSO₄ aqueous solution, saturated NaHCO₃ aqueous solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography with dichloromethane as eluent on silica gel to afford the title product. Yield: 425 mg (22%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 6.90 (m, 1H), 7.08 (dd, J= 5.08, 3.91 Hz, 1H), 7.26 (t, J = 10.35 Hz, 1H), 7.49 (m, 1H), 7.56 (dd, J = 3.71, 1.37 Hz, 1H), 7.63 (dd, J = 5.08, 1.37 Hz, 1H), 7.78 (dd, J = 6.35, 2.83Hz, 1H).

Step C. *N*-{4-[(Cyclohexylmethyl)amino]-3-nitrophenyl}thiophene-2-sulfonamide



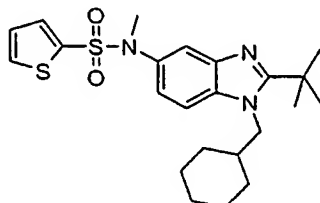
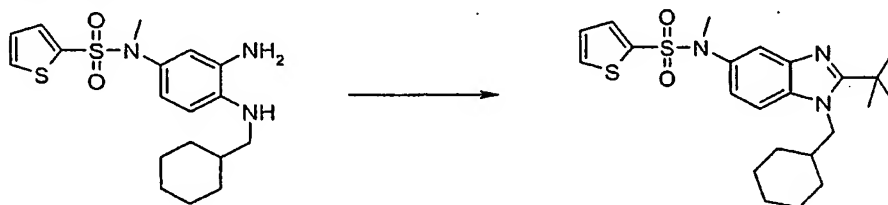
5 *N*-(4-Fluoro-3-nitrophenyl)thiophene-2-sulfonamide (73 mg, 0.241 mmol) and cyclohexylmethyl amine (0.040 mL, 0.289 mmol) were stirred in 3 mL of EtOH containing TEA (0.050 mL, 0.361 mmol) at 75°C for 6h. The solvent was evaporated. The crude product was dissolved in EtOAc and washed with 5% KHSO₄ solution, saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography using 2:1 / hexanes:EtOAc on silica gel. Yield: 60 mg (63%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.03 (m, 2H), 1.26 (m, 3H), 1.61 (m, 2H), 1.76 (m, 2H), 1.82 (m, 4H), 3.13 (dd, J = 6.64, 5.47Hz, 2H), 6.46 (m, 1H), 6.82 (d, J = 9.18Hz, 1H), 7.05 (dd, J = 4.98, 3.81Hz, 1H), 7.40 (dd, J = 9.18, 2.54Hz, 1H), 7.47 (dd, J = 3.71, 1.37Hz, 1H), 7.59 (dd, J = 5.08, 1.37Hz, 1H), 7.73 (d, J = 2.73Hz, 1H), 8.17 (m, 1H).

15 **Step D. *N*-(3-Amino-4-[(cyclohexylmethyl)amino]phenyl)thiophene-2-sulfonamide**



20 *N*-(4-[(Cyclohexylmethyl)amino]-3-nitrophenyl)thiophene-2-sulfonamide (60 mg, 0.152 mmol) was dissolved in 5 mL of DMF under nitrogen. Tin (II) chloride dihydrate (170 mg, 0.760 mmol) was added and the solution stirred at rt for 6h. More tin(II) chloride dihydrate (170 mg, 0.760 mmol) was added and the solution stirred at rt overnight. The reaction mixture was quenched by addition of saturated NaHCO₃ solution at 0°C. The solution was then extracted (2X) with EtOAc and washed with brine and dried over anhydrous MgSO₄. The product was used directly for Step A without further purification. Yield: 55 mg (99%); MS (ESI) (M+H)⁺ 366.14.

25

Example 2***N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylthiophene-2-sulfonamide****5 Step A. *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylthiophene-2-sulfonamide**

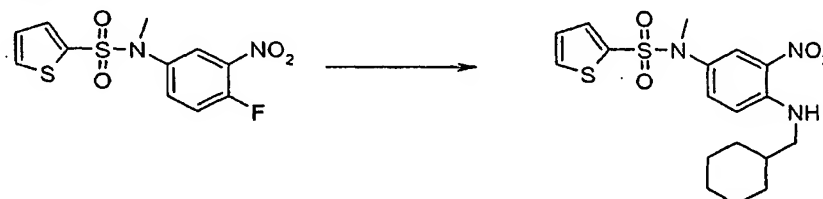
Following the procedure for Step A in Example 1, using *N*-{3-amino-4-[(cyclohexylmethyl) amino]phenyl} -*N*-methylthiophene-2-sulfonamide (115 mg, 0.303 mmol) (for preparation, see the following steps B, C and D) and trimethylacetyl chloride (0.041 mL, 0.333 mmol) in 3mL of DCE. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 65 mg (38%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.22 (m, 5 H), 1.61 (m, 2 H), 1.64 (s, 9 H), 1.67 (m, 1 H), 1.74 (m, 2 H), 2.08 (m, 1 H), 3.29 (s, 3 H), 4.43 (d, J=7.62 Hz, 2 H), 7.15 (dd, J=5.08, 3.71 Hz, 1 H), 7.33 (dd, J=8.98, 1.95 Hz, 1 H), 7.40 (dd, J=3.71, 1.37 Hz, 1 H), 7.55 (d, J=1.56 Hz, 1 H), 7.81 (dd, J=5.08, 1.37 Hz, 1 H), 7.85 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 446.1; Anal. Calcd for C₂₃H₃₁N₃O₂S₂ + 1.5 TFA + 0.1 H₂O: C, 50.49; H, 5.33; N, 6.79. Found: C, 50.55; H, 5.39; N, 6.76.

20

Step B. *N*-(4-Fluoro-3-nitrophenyl)-*N*-methylthiophene-2-sulfonamide

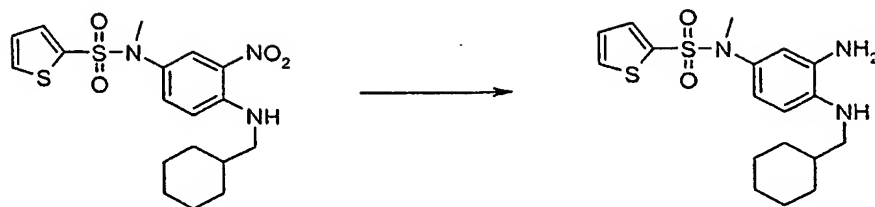
A solution of *N*-(4-fluoro-3-nitrophenyl)thiophene-2-sulfonamide (100 mg, 0.331 mmol) in MDF (1 mL) was added to a cold (0°C) stirring DMF solution (2 mL) of NaH (60% dispersion in oil) (20 mg, 0.496 mmol) under nitrogen. The solution was stirred at 0°C for 20 min. Methyl iodide (0.060 mL, 0.993 mmol) was added dropwise and the solution stirred at rt for 3h. The reaction mixture was quenched at 0°C by the slow addition of saturated NH₄Cl solution. The solvent was evaporated *in vacuo*. The crude product was dissolved in EtOAc and washed with saturated NaHCO₃ aqueous solution, brine and dried over anhydrous MgSO₄. The product was purified by flash chromatography with dichloromethane as eluent on silica gel to afford the title product. Yield: 78 mg (74%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 3.22 (s, 3H), 7.10 (dd, J = 4.98, 3.81Hz, 1H), 7.26 (dd, J = 3.91, 1.37Hz, 1H), 7.56 (m, 1H), 7.63 (dd, J = 5.08, 1.37Hz, 1H), 7.69 (dd, J = 6.44, 2.73Hz, 1H).

Step C. *N*-{4-[(Cyclohexylmethyl)amino]-3-nitrophenyl}-*N*-methylthiophene-2-sulfonamide



Following the procedure for Step C in Example 1, using *N*-(4-Fluoro-3-nitrophenyl)-*N*-methylthiophene-2-sulfonamide (3) (100 mg, 0.316 mmol), methylcyclohexylamine (0.050 mL, 0.379 mmol) and TEA (0.050 mL, 0.474 mmol) in 3 mL of EtOH. The product was used directly for the next step without any column chromatography purification. Yield: 130 mg (99%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 0.98 (m, 1H), 1.04 (m, 1H), 1.20 (m, 1H), 1.66 (m, 2H), 1.75 (m, 2H), 1.81 (d, J = 12.50Hz, 2H), 3.12 (m, 2H), 3.16 (s, 3H), 6.80 (d, J = 9.37Hz, 1H), 7.09 (dd, J = 4.98, 3.81Hz, 1H), 7.37 (dd, J = 3.81, 1.27Hz, 1H), 7.42 (dd, J = 9.28, 2.64Hz, 1H), 7.59 (dd, J = 4.98, 1.27Hz, 1H), 7.65 (d, J = 2.54Hz, 1H), 8.20 (m, 1H).

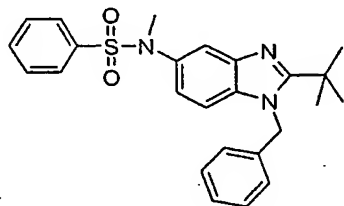
Step D. *N*-{3-Amino-4-[(cyclohexylmethyl)amino]phenyl}-*N*-methylthiophene-2-sulfonamide



Following the procedure for Step D in Example 1, using *N*-{4-[(cyclohexylmethyl)amino]-3-nitrophenyl}-*N*-methylthiophene-2-sulfonamide (125 mg, 0.305 mmol) and tin(II) chloride dihydrate (2X345 mg, 2X1.52 mmol). The product was used directly for Step A without further purification. Yield: 115 mg (99%); MS (ESI) (M+H)⁺ 379.97.

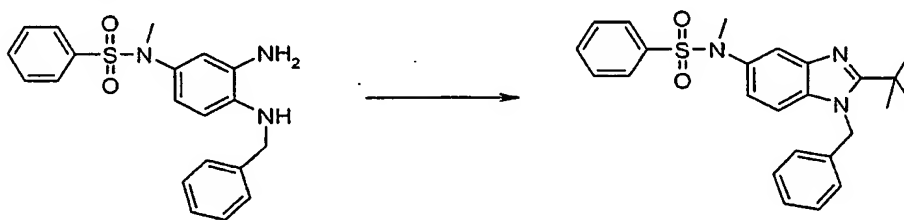
Example 3

N-(1-Benzyl-2-*tert*-butyl-1*H*-benzimidazol-5-yl)-*N*-methylbenzenesulfonamide



10

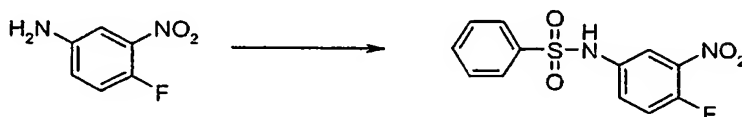
Step A. *N*-(1-Benzyl-2-*tert*-butyl-1*H*-benzimidazol-5-yl)-*N*-methylbenzenesulfonamide



Following the procedure for Step A in Example 1, using *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide (88mg, 0.239mmol), trimethylacetyl chloride (0.032mL, 0.262mmol) and DMAP (7.0mg, 0.060mmol) in 5 mL of dichloromethane. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 38 mg (29%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.62 (s, 9 H), 3.21 (s, 3 H), 5.93 (s, 2 H), 7.09 (m, 2 H), 7.12 (dd, J=8.98, 2.15 Hz, 1 H), 7.32 (m, 4 H), 7.48 (m, 4 H), 7.57 (dd, J=1.95, 0.59 Hz, 1 H),

7.62 (m, 1 H); MS (ESI) (M+H)⁺ 434.1; Anal. Calcd for C₂₅H₂₇N₃O₂S + 1.4 TFA + 0.2 H₂O: C, 55.95; H, 4.86; N, 7.04. Found: C, 55.90; H, 4.85; N, 7.06.

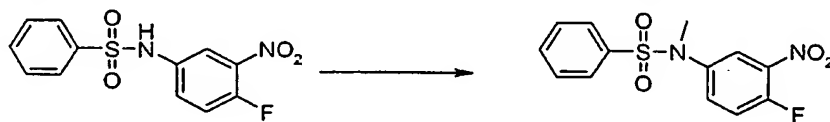
Step B. *N*-(4-Fluoro-3-nitrophenyl)benzenesulfonamide



4-Fluoro-3-nitroaniline (2.00 g, 12.8 mmol) was dissolved in 50 mL of pyridine containing a catalytic amount of DMAP. Benzenesulfonyl chloride (1.96 mL, 15.36 mmol) was added and the solution was stirred at rt for 3h. The solvent was evaporated. The crude product was dissolved in EtOAc and washed with 5% KHSO₄ solution, saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was purified by flash chromatography using 2:1 / hexanes:EtOAc on silica gel. Yield: 3.40 g (90%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 7.09 (m, 1H), 7.18 (dd, J= 9.96, 8.98 Hz, 1H), 7.40 (m, 1H), 7.48 (m, 2H), 7.58 (m, 1H), 7.71 (dd, J = 6.25, 2.73Hz, 1H), 7.76 (m, 2H).

15

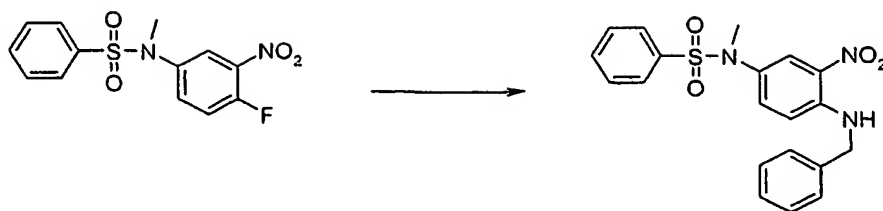
Step C. *N*-(4-Fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide



Following the procedure for Step B in Example 2, using *N*-(4-fluoro-3-nitrophenyl)benzenesulfonamide (1.00 g, 3.38 mmol), NaH (60% dispersion in oil) (160 mg, 4.06 mmol) and methyl iodide (0.315 mL, 5.07 mmol) in 25 mL of DMF. The product was purified by flash chromatography using dichloromethane as eluent on silica gel. Yield: 815 mg (78%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 3.19 (s, 3H), 7.28 (m, 1H), 7.51 (m, 1H), 7.54 (m, 2H), 7.57 (m, 1H), 7.65 (m, 2H).

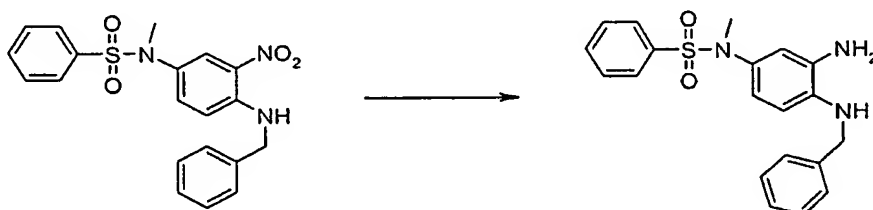
Step D. *N*-[4-(Benzylamino)-3-nitrophenyl]-*N*-methylbenzenesulfonamide

25



- Following the procedure for Step C in Example 1, using *N*-(4-fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide (71 mg, 0.229 mmol, benzylamine (0.030 mL, 0.275 mmol) and TEA (0.050 mL, 0.344 mmol) in 3 mL of EtOH. The product was used
- 5 directly for the next step without further purification. Yield: 99 mg (99%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 3.12 (s, 3H), 4.56 (d, *J* = 5.47 Hz, 2H), 6.81 (d, *J* = 9.18 Hz, 1H), 7.34 (m, 3H), 7.40 (m, 3H), 7.49 (m, 2H), 7.57 (m, 1H), 7.60 (m, 1H), 7.64 (dd, *J* = 4.30, 1.95 Hz, 1H), 8.47 (m, 1H).

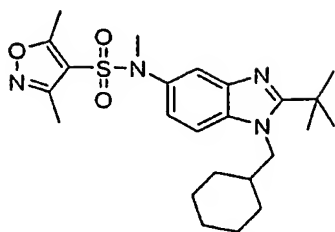
- 10 **Step E. *N*-[3-Amino-4-[(cyclohexylmethyl)amino]phenyl]-*N*-methylbenzenesulfonamide**



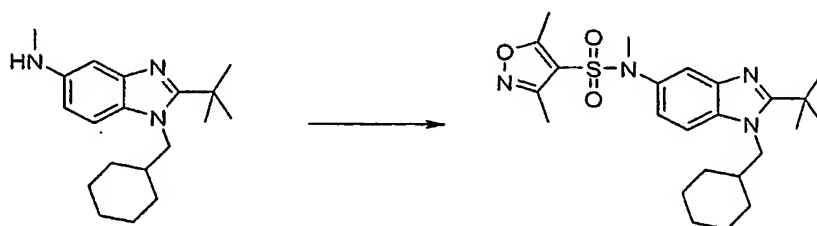
- N*-[4-(benzylamino)-3-nitrophenyl]-*N*-methylbenzenesulfonamide (95 mg, 0.239 mmol) was dissolved in 15 mL of EtOAc containing a catalytic amount of 10% Pd/C.
- 15 The solution was shaken in a Parr hydrogenation apparatus under H₂ atmosphere (40 psi) at rt for 4h. The solution was filtered through Celite and the solvent was evaporated. The product was used directly for Step A without further purification. Yield: 88 mg (99%); MS (ESI) (*M*+H)⁺ 367.97.

- 20 **Example 4**

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,3,5-trimethylisoxazole-4-sulfonamide



Step A. *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,3,5-trimethylisoxazole-4-sulfonamide



- 5 2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (35 mg, 0.117 mmol) (for preparation, see the following steps B, C, D, E and F) and 3,5-dimethylisoxazole-4-sulfonyl chloride (0.030 mg, 0.140 mmol) were stirred in 3 mL of dichloromethane containing a catalytic amount of DMAP overnight at rt. The solvent was evaporated. The product was purified by reversed-phase HPLC using 20-
10 80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 49 mg (73%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.21 (m, 5 H), 1.58 (m, 2 H), 1.65 (s, 10 H), 1.74 (m, 2 H), 1.88 (s, 3 H), 2.08 (m, 1 H), 2.33 (s, 3 H), 3.31 (s, 3 H), 4.46 (d, J=7.81 Hz, 2 H), 7.47 (dd, J=8.98, 1.95 Hz, 1 H), 7.68 (d, J=1.76 Hz, 1 H), 7.91 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 459.2;
15 Anal. Calcd for C₂₄H₃₄N₄O₃S + 1.6 TFA + 0.2 H₂O: C, 50.68; H, 5.63; N, 8.69. Found: C, 50.70; H, 5.65; N, 8.81.

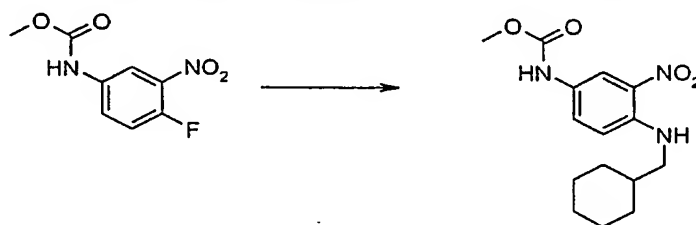
Step B. Methyl (4-fluoro-3-nitrophenyl)carbamate



- 20 Methyl chloroformate (13.2 mL, 170.2 mmol) was added dropwise to a cold (0°C) dichloromethane (200 mL) solution of 4-fluoro-3-nitro aniline (24.15 g, 154.7 mmol)

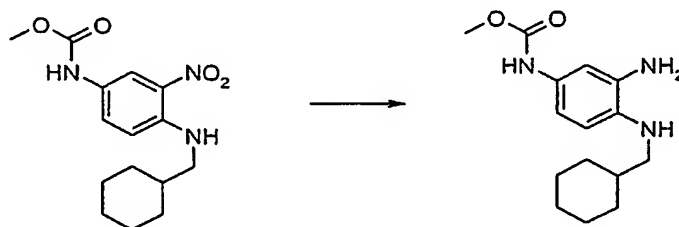
and DIPEA (35 mL, 201 mmol). The reaction mixture was stirred at rt overnight. The solution was then diluted with 200 mL of dichloromethane and washed with 2M HCl, brine and dried over anhydrous MgSO_4 . The solvent was concentrated and the product was directly used for next step without further purification. Yield: 35.5 g (99%); ^1H NMR (400 MHz, CHLOROFORM-D) δ 3.81 (s, 3 H), 7.02 (s, 1 H), 7.23 (m, 1 H), 7.72 (d, $J=8.59$ Hz, 1 H), 8.17 (dd, $J=6.35, 2.64$ Hz, 1 H).

Step C. Methyl {4-[(cyclohexylmethyl)amino]-3-nitrophenyl}carbamate



Methyl (4-fluoro-3-nitrophenyl)carbamate (1.00 g, 4.67 mmol) and cyclohexylmethyl amine (0.730 mL, 5.60 mmol) were stirred in EtOH (20 mL) containing TEA (1.0 mL, 7.00 mmol) at 75°C for 24h. The solvent was concentrated. The residue was dissolved in EtOAc and washed with 5% KHSO_4 solution, saturated NaHCO_3 solution, brine and dried over anhydrous MgSO_4 . The crude product was purified by flash chromatography using 4:1/hex:EtOAc on silica gel. Yield: 1.05 g (73%); ^1H NMR (400 MHz, CHLOROFORM-D) δ 1.04 (ddd, $J = 24.02, 12.11, 2.93$ Hz, 2H), 1.25 (m, 3H), 1.69 (m, 2H), 1.76 (m, 1H), 1.79 (m, 1H), 1.83 (m, 1H), 1.86 (m, 1H), 3.14 (dd, $J = 6.44, 5.66$ Hz, 2H), 3.78 (s, 3H), 6.46 (m, 1H), 6.84 (d, $J = 9.37$ Hz, 1H), 7.63 (m, 1H), 8.05 (d, $J = 2.54$ Hz, 1H), 8.09 (m, 1H).

Step D. Methyl {3-amino-4-[(cyclohexylmethyl)amino]phenyl}carbamate

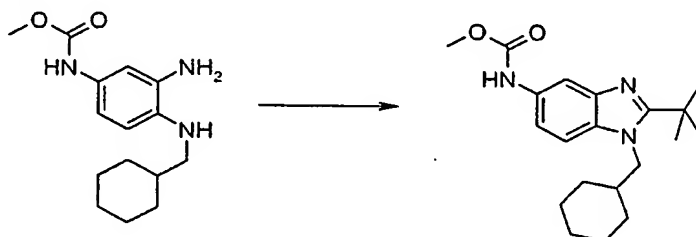


Methyl {4-[(cyclohexylmethyl)amino]-3-nitrophenyl}carbamate (1.05 g, 3.42 mmol) was dissolved in 30 mL of EtOAc containing a catalytic amount of 10% Pd/C. The

solution was shaken in a Parr hydrogenation apparatus under H₂ atmosphere (40 psi) at rt overnight. The solution was filtered through Celite and the solvent was evaporated. The product was directly used for the next step without further purification. Yield: 950 mg (99%). MS (ESI) (M+H)⁺ 277.9.

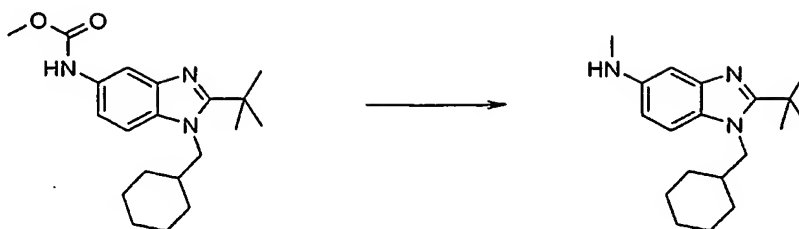
5

Step E. Methyl [2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbamate



Methyl {3-amino-4-[(cyclohexylmethyl)amino]phenyl}carbamate (950 mg, 3.43 mmol) and DMAP (100 mg, 0.858 mmol) were dissolved in 25 mL of dichloromethane. Trimethylacetyl chloride (0.460 mL, 3.77 mmol) was added dropwise and the solution was stirred at rt for 1h. The solvent was concentrated. The residue was divided in two portions and each of them was dissolved in 3 mL of glacial AcOH in a sealed tube. The solutions were heated at 150°C using a Personal Chemistry Smith Synthesizer microwave instrument for three intervals of 30 min (3 X 30 min). The contents of the two tubes were combined and the solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography using 3:1/dichloromethane:diethyl ether. Yield: 656 mg (56%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.08 (m, 2H), 1.18 (m, 3H), 1.54 (s, 9H), 1.65 (m, 1H), 1.69 (m, 2H), 1.73 (dd, J = 5.96, 3.22 Hz, 2H), 2.02 (m, 1H), 3.78 (s, 3H), 4.10 (d, J = 7.42 Hz, 2H), 6.64 (m, 1H), 7.25 (d, J = 8.79 Hz, 1H), 7.39 (m, 1H), 7.59 (d, J = 1.76 Hz, 1H).

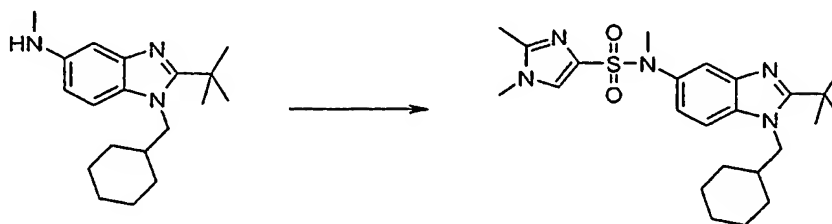
Step F. 2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine



Methyl [2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbamate (650 mg, 1.89 mmol) was dissolved in 20 mL of THF at 0°C under nitrogen. 1M HCl/ether (2.65 mL, 2.65 mmol) was added dropwise and the solution was stirred at 0°C for 15 min. LiAlH₄ (360 mg, 9.45 mmol) was then slowly added and the solution was stirred at rt overnight. The reaction mixture was quenched at 0°C by addition of MeOH (5 mL) followed by water (10 mL). The solution was diluted with EtOAc and washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated and the product was used directly for Step A without further purification. Yield: 544 mg (96%). ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.08 (s, 2 H) 1.17 (m, 3 H) 1.54 (s, 9 H) 1.64 (m, 2 H) 1.67 (m, 2 H) 1.72 (m, 2 H) 2.02 (m, 1 H) 2.87 (s, 3 H) 4.06 (d, *J*=7.62 Hz, 2 H) 6.60 (dd, *J*=8.69, 2.25 Hz, 1 H) 7.00 (d, *J*=1.76 Hz, 1 H) 7.12 (d, *J*=8.59 Hz, 1 H).

Example 5

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,1,2-trimethyl-1*H*-imidazole-4-sulfonamide

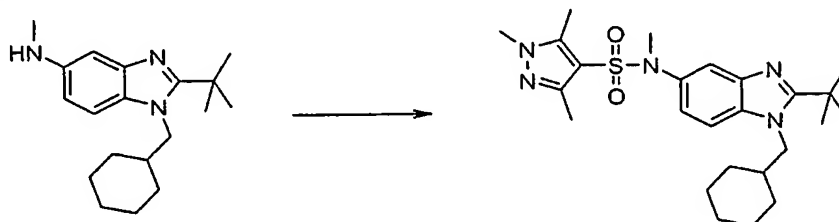


Following the procedure for Step A in Example 4, using 2-*tert*-butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (19) (36 mg, 0.120 mmol), 1,2-dimethyl-1*H*-imidazole-4-sulfonyl chloride (30 mg, 0.144 mmol) and DMAP (catalytic) in 3 mL of dichloromethane. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 47 mg (69%); ¹H NMR (400 MHz,

METHANOL-D₄) δ 1.22 (m, 5 H), 1.62 (m, 2 H), 1.64 (s, 9 H), 1.67 (m, 1 H), 1.75 (m, 2 H), 2.09 (m, 1 H), 2.34 (s, 3 H), 3.28 (s, 3 H), 3.61 (s, 3 H), 4.43 (d, J=7.62 Hz, 2 H), 7.43 (dd, J=8.98, 2.15 Hz, 1 H), 7.51 (s, 1 H), 7.66 (d, J=1.95 Hz, 1 H), 7.82 (d, J=9.18 Hz, 1 H); MS (ESI) (M+H)⁺ 458.2; Anal. Calcd for C₂₄H₃₅N₅O₂S + 1.7 TFA + 0.1 H₂O: C, 50.38; H, 5.69; N, 10.72. Found: C, 50.39; H, 5.73; N, 10.73.

Example 6

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,1,3,5-tetramethyl-1*H*-pyrazole-4-sulfonamide



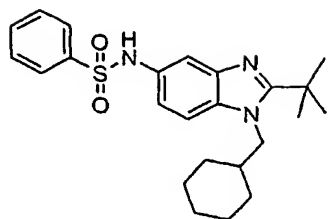
10

Following the procedure for Step A in Example 4, using 2-*tert*-butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (19) (36 mg, 0.120 mmol), 1,3,5-trimethyl-1*H*-pyrazole-4-sulfonyl chloride (30 mg, 0.144 mmol) and DMAP (catalytic) in 3mL of dichloromethane. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 49 mg (70%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.20 (m, 5 H), 1.56 (m, 2 H), 1.65 (s, 9 H), 1.67 (m, 1 H), 1.74 (m, 2 H), 1.80 (s, 3 H), 2.08 (m, 1 H), 2.16 (s, 3 H), 3.21 (s, 3 H), 3.69 (s, 3 H), 4.44 (d, J=7.81 Hz, 2 H), 7.38 (dd, J=9.08, 2.05 Hz, 1 H), 7.62 (d, J=1.56 Hz, 1 H), 7.84 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 472.2; Anal. Calcd for C₂₅H₃₇N₅O₂S + 1.2 TFA + 0.4 H₂O: C, 53.45; H, 6.38; N, 11.37. Found: C, 53.50; H, 6.38; N, 11.29.

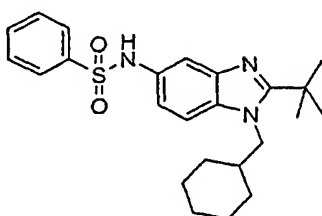
20

Example 7

N-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]benzene sulfonamide

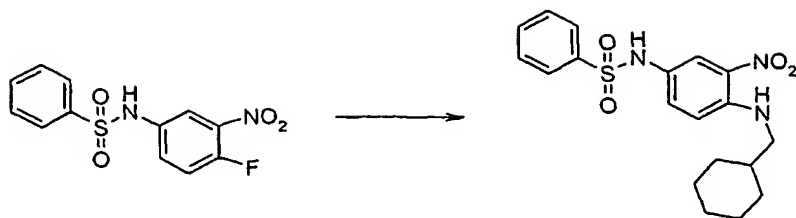


Step A. *N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



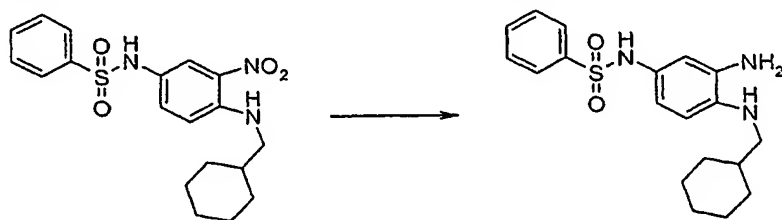
- 5 DMAP (44.0 mg, 0.36 mmol) and then trimethylacetyl chloride (199.0 mg, 1.65 mmol) at 0 °C was added into a solution of *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzenesulfonamide (540.1 mg, 1.5 mmol) (for preparation, see the following steps B and C) in dichloromethane (40 mL). The mixture was stirred for 5 h at room temperature. After evaporation of the solvent, the
- 10 residue was dissolved in 1,2-dichloroethane (5x5 mL) in five Teflon-capped test tubes. The vessels were irradiated by microwave for 2h at 170 °C. The combined reaction mixture diluted with EtOAc (100 mL), washed with 2N NaOH(10 mL), sat. NaCl (10 mL) and dried over Na₂SO₄. After filtration and evaporation, the residue was purified by MPLC (hex/EtOAc 1:1 on silica gel) to give 568.2 mg (89%) of a
- 15 white solid as the title compound. Part of the product was converted to TFA salt. ¹HNMR (400 MHz, CD₃OD): δ 1.18 (m, 5 H), 1.55 (m, 2 H), 1.59 (s, 9 H), 1.65 (m, 1 H), 1.71 (m, 2 H), 2.03 (m, 1 H), 4.34 (d, J=7.42 Hz, 2 H), 7.20 (d, J=9.18 Hz, 1 H), 7.44 (m, 2 H), 7.53 (m, 1 H), 7.58 (s, 1 H), 7.70 (d, J=8.79 Hz, 1 H), 7.76 (d, J=7.42 Hz, 2 H). MS (ESI) (M+H)⁺ = 426.1. Anal. Calcd for C₂₄H₃₁N₃O₂S+1.10 TFA+0.10
- 20 H₂O: C, 56.92; H, 5.89; N, 7.60. Found: C, 56.95; H, 5.92; N, 7.56.

Step B: *N*-{4-[(cyclohexylmethyl)amino]-3-nitrophenyl}benzenesulfonamide

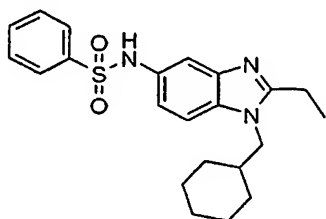


Cyclohexylmethylamine (3.48 mL, 3.03 g, 26.7 mmol) was added to a mixture of *N*-(4-fluoro-3-nitrophenyl)benzenesulfonamide (3.60 g, 12.1 mmol) in 60 mL of EtOH-H₂O (1:1 V/V) at room temperature. The reaction mixture was heated for 48 h at 60 °C, and allowed to cool to room temperature and concentrated to a small volume, and then extracted with EtOAc. The crude product was purified by MPLC using Hex/EtOAc (4:1) on silica gel to give 3.75 g (79%) of an orang-red solid as the title compound. ¹HNMR (400 MHz, CD₃Cl): δ 1.05 (m, 2 H), 1.24 (m, 3 H), 1.72 (m, 6 H), 3.12 (dd, *J*=6.64, 5.47 Hz, 2 H), 6.23 (s, 1 H), 6.79 (d, *J*=9.18 Hz, 1 H), 7.36 (dd, *J*=9.08, 2.64 Hz, 1 H), 7.48 (m, 2 H), 7.58 (m, 1 H), 7.63 (d, *J*=2.54 Hz, 1 H), 7.72 (m, 2 H), 8.14 (s, 1 H).

Step C: *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzenesulfonamide



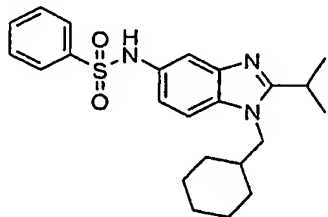
N-{4-[(cyclohexylmethyl)amino]-3-nitrophenyl}benzenesulfonamide (3.75 g, 9.63 mmol) was hydrogenated in ethyl acetate (200 mL) catalyzed by 10% Pd/C (0.5 g) at 30-40 psi H₂ in Parr shaker for 20 h at room temperature. After filtration through Celite and concentration, 4.0 g (100%) of a light yellow solid was obtained as the title compound, which was used for Step A without further purification. ¹HNMR (400 MHz, CD₃Cl): δ 0.88 (m, 1 H), 0.99 (m, 2 H), 1.23 (m, 3 H), 1.56 (m, 1 H), 1.75 (m, 4 H), 2.86 (d, *J*=6.64 Hz, 2 H), 3.33 (s broad, 3 H), 6.30 (s broad, 1 H), 6.33 (dd, *J*=8.30, 2.44 Hz, 1 H), 6.41 (m, 1 H), 6.56 (d, *J*=2.34 Hz, 1 H), 7.41 (m, 2 H) 7.52 (m, 1 H), 7.70 (m, 2 H). MS (ESI) (M-H)⁺: 359.89.

Example 8***N*-[1-(cyclohexylmethyl)-2-ethyl-1*H*-benzimidazol-5-yl]benzenesulfonamide**

- DMAP (15.0 mg, 0.12 mmol) and then propionyl chloride (50.9 mg, 0.55 mmol) was added into a solution of *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl} benzene sulfonamide (180.3 mg, 0.5 mmol) in dichloromethane (15 mL) at 0 °C. The mixture was stirred for 5 h at room temperature. After evaporation of the solvent, the residue was dissolved in acetic acid (10 mL) and then heated for 20 h at 80°C. Upon concentration, the residue diluted with EtOAc (100 mL), washed with 2N NaOH (10 mL), sat. NaCl (10 mL) and dried over Na₂SO₄. The crude product was purified by MPLC (hexane/EtOAc 1:9 on silica gel) to give 157.7 mg (79%) of a white solid as the title compound. Part of the product was converted to TFA salt. ¹HNMR (400 MHz, CD₃OD): δ 1.12 (m, 2 H), 1.21 (m, 3 H), 1.48 (t, J=7.62 Hz, 3 H), 1.60 (m, 2 H), 1.68 (m, 1 H), 1.73 (m, 2 H), 1.90 (m, 1 H), 3.18 (q, J=7.49 Hz, 2 H), 4.19 (d, J=7.62 Hz, 2 H), 7.24 (m, 1 H), 7.47 (m, 2 H), 7.56 (m, 2 H), 7.71 (d, J=8.98 Hz, 1 H), 7.79 (m, 2 H). MS (ESI) (M+H)⁺ = 398.1.

Example 9

- N*-[1-(cyclohexylmethyl)-2-isopropyl-1*H*-benzimidazol-5-yl]benzene sulfonamide**

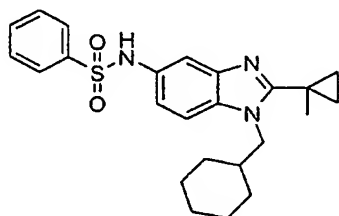


Following the procedure for Step A in Example 7, using *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl} benzene sulfonamide (182.1 mg, 0.5 mmol), DMAP (15.0 mg, 0.12 mmol) and isobutyryl chloride (50.2 mg, 0.56 mmol) CH₂Cl₂

(15 mL). The crude product was purified by MPLC (Hex/EtOAc 1:1). Yield: 178.4 mg (86%). ¹HNMR (400 MHz, CD₃OD): δ 1.17 (m, 5 H), 1.47 (d, J=6.83 Hz, 6 H), 1.60 (m, 2 H), 1.72 (m, 3 H), 1.88 (m, 1 H), 3.62 (m, 1 H), 4.25 (d, J=7.62 Hz, 2 H), 7.25 (dd, J=8.88, 2.05 Hz, 1 H), 7.48 (m, 2 H), 7.57 (m, 2 H), 7.73 (d, J=8.98 Hz, 1 H), 7.80 (m, 2 H). MS (ESI) (M+H)⁺ = 412.1.

Example 10

N-[1-(cyclohexylmethyl)-2-(1-methylcyclopropyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



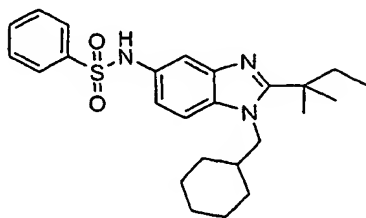
10

Diisopropylethylamine (104.7 mg, 0.81 mmol) was added into a solution of *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzene sulfonamide (195.6 mg, 0.543 mmol), and 1-methylcyclopropanecarboxylic acid (59.8 mg, 0.6 mmol) in DMF (5 mL) at 0 °C. Stirring for 20 min. HATU (246.4 mg, 0.65 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, diluted with water (100 mL), and extracted with EtOAc (2x50 mL). The combined organic phases were washed with NaCl (20 mL) and dried with anhydrous sodium sulphate. After filtration and concentration, the residue was dissolved in acetic acid (10 mL) and heated for 20 h at 80 °C. Upon evaporation of the solvent, 93.7 mg of the acetate salt was lyophilized, and the rest was diluted with EtOAc (100 mL), washed with 2N NaOH(10 mL), sat. NaCl (2x10 mL) and dried over anhydrous sodium sulphate. After filtration and evaporation, 144.9 mg of the free amine as the title compound was obtained. Total yield: 99%. ¹HNMR (400 MHz, CD₃OD): δ 0.89 (m, 2 H), 1.10 (m, 4 H), 1.21 (m, 3 H), 1.45 (s, 3 H), 1.55 (d, 2 H), 1.69 (m, 3H), 2.08 (m, 1 H), 4.13 (d, J=7.62 Hz, 2 H), 7.01 (dd, J=8.79, 1.95 Hz, 1 H,) 7.25 (d, J=1.95 Hz, 1 H), 7.35 (d, J=8.79 Hz, 1 H), 7.40 (t, J=7.62 Hz, 2 H), 7.50 (t, J=7.42 Hz, 1 H), 7.68 (d, J=7.42 Hz, 2 H). MS (ESI) (M+H)⁺ = 424.1. Anal. Calcd for C₂₄H₂₉N₃O₂S+0.4 AcOH+0.10 H₂O: C, 65.92; H, 6.98; N, 9.45. Found: C, 66.01; H, 6.89; N, 9.09.

25

Example 11

***N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide**



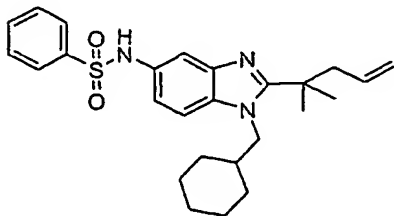
5

Following the procedure in Example 10, using *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzene sulfonamide (180.3 mg, 0.50 mmol), 2,2-dimethylbutyric acid (63.9 mg, 0.55 mmol), diisopropylethylamine (96.6 mg, 0.75 mmol) and HATU (228.1 mg, 0.60 mmol) in DMF (5 mL) and then in acetic acid (10 mL), the crude product was purified by reversed HPLC using 30-80% CH₃CN/H₂O to give 39.9 mg (14%) of a white solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 0.81 (t, J=7.52 Hz, 3 H), 1.20 (m, 5 H), 1.58 (m, 2 H), 1.62 (s, 6 H), 1.68 (m, 1 H), 1.75 (m, 2 H), 1.97 (q, J=7.62 Hz, 2 H), 2.03 (m, 1 H), 4.37 (d, J=7.62 Hz, 2 H), 7.23 (dd, J=8.98, 1.95 Hz, 1 H), 7.47 (m, 2 H), 7.56 (m, 1 H), 7.59 (m, 1 H), 7.73 (d, J=8.98 Hz, 1 H), 7.80 (m, 2 H). MS (ESI) (M+H)⁺ = 440.2. Anal. Calcd for C₂₅H₃₃N₃O₂S+1.0 TFA+0.60 H₂O: C, 57.45; H, 6.29; N, 7.44. Found: C, 57.49; H, 6.39; N, 7.35.

15

Example 12

***N*-[1-(cyclohexylmethyl)-2-(1,1-dimethyl-3-butenyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide**



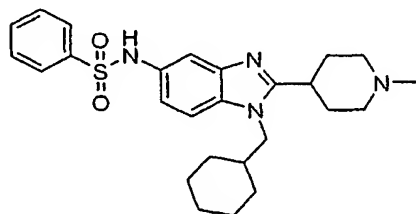
Following the procedure in Example 10, using *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzene sulfonamide (180.3 mg, 0.50 mmol), 2,2-

dimethyl-4-pentenoic acid (70.5 mg, 0.55 mmol), diisopropylethylamine (96.6 mg, 0.75 mmol) and HATU (228.1 mg, 0.60 mmol) in DMF (5 mL) and then in acetic acid (10 mL), the crude product was purified by reversed HPLC using 30-80% CH₃CN/H₂O to give 38.2 mg (14%) of a white solid as the title compound. ¹HNMR (400MHz, CD₃OD): δ 1.19 (m, 5 H), 1.59 (m, 2 H), 1.65 (s, 6 H), 1.68 (m, 1 H), 1.74 (m, 2 H), 2.04 (m, 1 H), 2.67 (d, J=7.42 Hz, 2 H), 4.40 (d, J=7.62 Hz, 2 H), 5.03 (s, 1 H), 5.07 (m, 1 H), 5.60 (m, 1 H), 7.23 (dd, J=8.98, 2.15 Hz, 1 H), 7.47 (m, 2 H), 7.56 (m, 1 H), 7.59 (d, J=1.56 Hz, 1 H), 7.74 (d, J=8.98 Hz, 1 H), 7.80 (m, 2 H). MS (ESI) (M+H)⁺ = 452.2. Anal. Calcd for C₂₆H₃₃N₃O₂S+1.2 TFA: C, 57.97; H, 5.86; N, 7.14.

10 Found: C, 58.00; H, 5.74; N, 7.06.

Example 13

N-[1-(cyclohexylmethyl)-2-(1-methyl-4-piperidinyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide



15

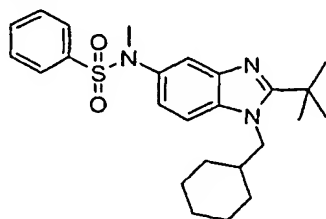
Following the procedure in Example 10: using *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzene sulfonamide (180.3 mg, 0.50 mmol), 1-methylpiperidine 4-carboxylic acid hydrochloride (98.8 mg, 0.55 mmol), diisopropylethylamine (161.6 mg, 1.25 mmol) and HATU (228.1 mg, 0.60 mmol) in DMF (5 mL) and then in acetic acid (10 mL), the crude product was purified by MPLC using CH₂Cl₂/MeOH (10:1) on silica gel to give 213.2 mg (91%) of a colorless syrup as the title compound. Part of the product was converted to TFA salt. ¹HNMR (400 MHz, CD₃OD): δ 1.08 (m, 2 H), 1.18 (m, 3 H), 1.52 (m, 2 H), 1.68 (m, 3 H), 1.79 (m, 1 H), 2.15 (m, 4 H), 2.91 (s, 3 H), 3.18 (m, 2 H), 3.35 (m, 1 H), 3.62 (d, J=13.28 Hz, 2 H), 4.08 (d, J=7.81 Hz, 2 H), 7.04 (dd, J=8.79, 1.95 Hz, 1 H), 7.40 (m, 4 H), 7.50 (m, 1 H), 7.69 (m, 2 H). MS (ESI) (M+H)⁺ = 467.2. Anal. Calcd for C₂₆H₃₄N₄O₂S+1.5 TFA+0.9 H₂O: C, 53.27; H, 5.75; N, 8.57. Found: C, 53.32; H, 5.5.69; N, 8.55.

20

25

Example 14

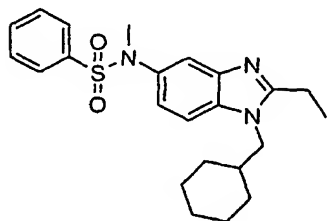
***N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzenesulfonamide**



- 5 NaH (54.0 mg, 60%, 1.34 mmol) was added to a solution of of *N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]benzene sulfonamide (258.5 mg, 0.607 mmol) in THF (15 mL) at 0 °C. After stirring for 1h, MeI (259.8 mg, 1.83 mmol) was added. The mixture was stirred overnight at room temperature, quenched with sat.
- 10 NaHCO₃ (5 mL). The two phases were separated. The aqueous was extracted with EtOAc (3x20 ml). The combined organic phases were washed with NaHCO₃ (2x10 mL) and dried with Na₂SO₄. After concentration, the residue was purified by MPLC using hex/EtOAc (1:1) on silica gel to give 216.5 mg (81%) of the title product, and converted to TFA salt as a white solid. ¹HNMR (400 MHz, CD₃OD): δ 1.20 (m, 5
- 15 H), 1.60 (m, 2 H), 1.64 (s, 9 H), 1.67 (m, 1 H), 1.75 (m, 2 H), 2.07 (m, 1 H), 3.24 (s, 3 H), 4.42 (d, J=7.62 Hz, 2 H), 7.26 (dd, J=8.98, 2.15 Hz, 1 H), 7.50 (m, 5 H), 7.65 (m, 1 H), 7.81 (d, J=9.18 Hz, 1 H). MS (ESI) (M+H)⁺ = 440.2. Anal. Calcd for C₂₅H₃₃N₃O₂S+1.20 TFA: C, 57.09; H, 5.98; N, 7.29. Found: C, 57.07; H, 6.01; N, 7.25.
- 20

Example 15

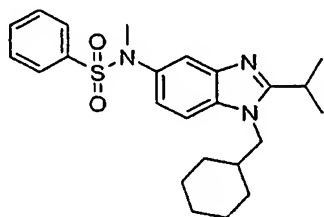
***N*-[1-(cyclohexylmethyl)-2-ethyl-1*H*-benzimidazol-5-yl]-*N*-methyl-benzene sulfonamide**



Following the procedure in Example 14, using *N*-[1-(cyclohexylmethyl)-2-ethyl-1*H*-benzimidazol-5-yl]benzenesulfonamide (91.3 mg, 0.23 mmol), sodium hydride (28.2 mg, 60%, 0.71 mmol) and iodomethane (97.9 mg, 0.69 mmol) in THF (10 mL). Yield: 69.7 mg (74%); white solid for TFA salt. ¹HNMR (400 MHz, CD₃OD): δ 1.20 (m, 5 H), 1.51 (t, J=7.52 Hz, 3 H), 1.65 (m, 2 H), 1.70 (m, 1 H), 1.76 (m, 2 H), 1.95 (m, 1 H), 3.22 (q, J=7.62 Hz, 2 H), 3.27 (s, 3 H), 4.26 (d, J=7.62 Hz, 2 H), 7.29 (dd, J=8.88, 2.05 Hz, 1 H), 7.50 (d, J=1.95 Hz, 1 H), 7.54 (m, 4 H), 7.67 (m, 1 H), 7.80 (d, J=8.98 Hz, 1 H). MS (ESI) (M+H)⁺ = 412.1

10 Example 16

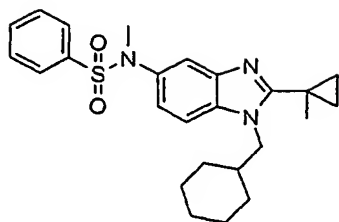
N-[1-(cyclohexylmethyl)-2-isopropyl-1*H*-benzimidazol-5-yl]-*N*-methyl-benzene sulfonamide



Following the procedure in Example 14, using *N*-[1-(cyclohexylmethyl)-2-isopropyl-1*H*-benzimidazol-5-yl]benzenesulfonamide (81.8 mg, 0.199 mmol), sodium hydride (24.0 mg, 60%, 0.596 mmol) and iodomethane (84.7 mg, 0.597 mmol) in THF (15 mL). Yield: 80.1 mg (95%); The title compound was converted to white solid as a TFA salt. ¹HNMR (400 MHz, CD₃OD): δ 1.20 (m, 5 H), 1.51 (d, J=6.83 Hz, 6 H), 1.64 (m, 2 H), 1.69 (m, 1 H), 1.76 (m, 2 H), 1.93 (m, 1 H), 3.27 (s, 3 H), 3.67 (m, 1 H), 4.31 (d, J=7.62 Hz, 2 H), 7.28 (m, 1 H), 7.54 (m, 5 H), 7.68 (m, 1 H), 7.81 (d, J=8.98 Hz, 1 H). MS (ESI) (M+H)⁺ = 426.1.

Example 17

N-[1-(cyclohexylmethyl)-2-(1-methylcyclopropyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzenesulfonamide

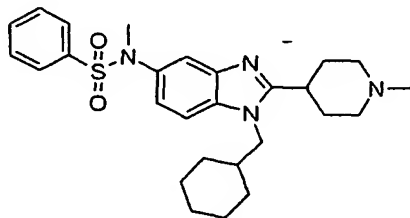


Following the procedure in Example 14, using *N*-[1-(cyclohexylmethyl)-2-(1-methylcyclopropyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (144.9 mg, 0.342 mmol), sodium hydride (30.0 mg, 60%, 0.752 mmol) and iodomethane (145.7 mg, 1.03 mmol) in THF (15 mL). Yield: 72.3 mg (48%); compound was converted to a white solid as a TFA salt. ¹HNMR (400 MHz, CD₃OD): δ 1.19 (m, 4 H), 1.26 (m, 3 H), 1.34 (m, 2 H), 1.59 (s, 3 H), 1.71 (m, 5 H), 2.19 (m, 1 H), 3.26 (s, 3 H), 4.38 (d, J=7.81 Hz, 2 H), 7.29 (dd, J=9.08, 2.05 Hz, 1 H), 7.50 (m, 1 H), 7.52 (m, 1 H), 7.55 (m, 3 H), 7.67 (m, 1 H), 7.83 (d, J=8.98 Hz, 1 H). MS (ESI) (M+H)⁺ = 438.2. Anal.

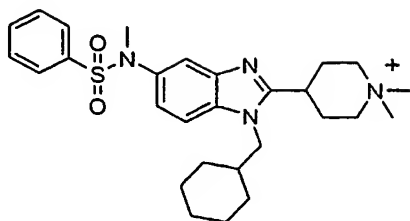
Calcd for C₂₅H₃₁N₃O₂S+1.2 TFA+0.10 H₂O: C, 57.11; H, 5.67; N, 7.29. Found: C, 57.19; H, 5.74; N, 7.22.

Example 18 and 19

Example 18: *N*-[1-(cyclohexylmethyl)-2-(1-methyl-4-piperidinyl)-1*H*-benzimidazol-5-yl]-*N*-methyl- benzenesulfonamide



Example 19: 4-[1-(cyclohexylmethyl)-5-[methyl(phenylsulfonyl)amino]-1*H*-benzimidazol-2-yl]-1,1-dimethyl- piperidinium

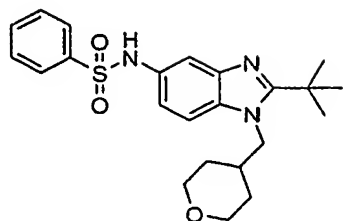


Following the procedure in Example 14: using *N*-[1-(cyclohexylmethyl)-2-(1-methyl-4-piperidiny)]-1*H*-benzimidazol-5-yl]- benzenesulfonamide (97.3 mg, 0.209 mmol),
 5 sodium hydride (18.4 mg, 60%, 0.459 mmol) and iodomethane/THF (1.0 M, 250 μ L, 0.25 mmol) in THF (15 mL), the crude product was purified by reversed HPLC using 15-60% CH₃CN/H₂O to give the title compounds A and B as following:

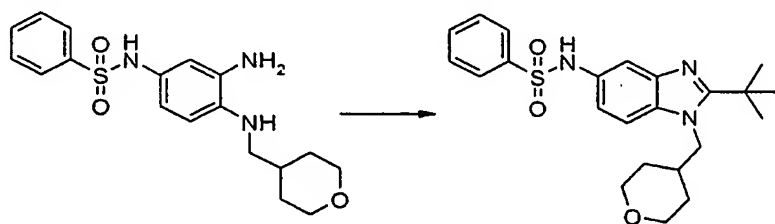
- 1) Compound A: *N*-[1-(cyclohexylmethyl)-2-(1-methyl-4-piperidiny)]-1*H*-benzimidazol-5-yl]-*N*-methyl- benzenesulfonamide. Yield: 36.8 mg (30%) The
 10 compound was converted to TFA salt as a white solid. ¹HNMR (400 MHz, CD₃OD): δ 1.10 (m, 2 H), 1.18 (m, 3 H), 1.55 (m, 2 H), 1.69 (m, 3 H), 1.81 (m, 1 H), 2.15 (m, 2 H), 2.38 (m, 2 H), 3.23 (s, 6 H), 3.46 (m, 1 H), 3.57 (m, 2 H), 3.66 (m, 2 H), 4.14 (d, J =7.62 Hz, 2 H), 7.13 (m, 1 H), 7.43 (m, 3 H), 7.51 (m, 2 H), 7.72 (m, 2 H). (M+H)⁺ = 481.2. Anal. Calcd for C₂₇H₃₆N₄O₂S+3.2 TFA+0.5 H₂O: C, 46.94; H, 4.74; N, 6.56.
 15 Found: C, 46.97; H, 4.76; N, 6.51.
- 2) Compound B: 4-[1-(cyclohexylmethyl)-5-[methyl(phenylsulfonyl)amino]-1*H*-benzimidazol-2-yl]-1,1-dimethyl- piperidinium. Yield: 41.1 mg (32%). TFA salt, white solid,. ¹HNMR (400 MHz, CD₃OD): δ 1.14 (m, 2 H), 1.23 (m, 3 H), 1.59 (m, 2 H), 1.72 (m, 3 H), 1.86 (m, 1 H), 2.18 (m, 2 H), 2.43 (m, 2 H), 3.25 (s, 3 H), 3.26 (s, 6
 20 H,) 3.46 (m, 1 H,) 3.58 (m, 2 H), 3.69 (m, 2 H), 4.18 (d, J =7.62 Hz, 2 H), 7.11 (dd, J =8.79, 1.95 Hz, 1 H), 7.35 (d, J =1.95 Hz, 1 H), 7.50 (m, 1 H), 7.55 (m, 4 H), 7.66 (m, 1 H). MS (ESI) (M+H)⁺: 495.2.

Example 20

- 25 *N*-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-benzenesulfonamide



Step A. *N*-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-benzenesulfonamide

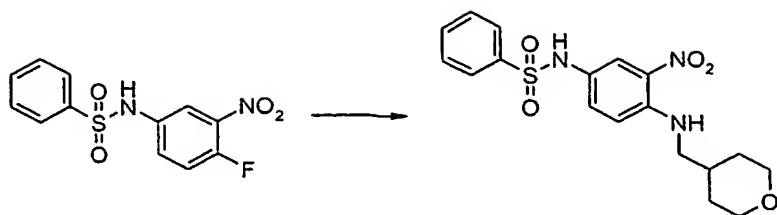


5

Catalytic DMAP in one portion and pivaloyl chloride (0.26 mL, 1.1 eq) were added dropwise sequentially to a stirring solution of *N*-[3-amino-4-[(tetrahydro-2*H*-pyran-4-yl)methyl]amino] phenyl]-benzenesulfonamide (705.2 mg, 1.95 mmol) (for preparation, see Steps B and C) in CH₂Cl₂ (100 mL) at 0°C. The solution was stirred for 2 hours, then the solvent was concentrated, and the residue was re-dissolved in AcOH (2 mL). The resulting solution was heated at 150°C for 1800 s using microwave irradiation and the solvent was then concentrated. The residue was re-dissolved in EtOAc, washed with 1N NaOH (2X) and brine and dried over anhydrous Na₂SO₄. Purification by MPLC using EtOAc followed by reversed-phase HPLC using 10-90% MeCN in H₂O afforded the title compound as a colourless solid (16.3 mg, 2% yield); ¹H NMR (400 MHz, CD₃OD) δ 1.46-1.55 (m, 4 H), 1.62 (s, 9 H), 2.25-2.35 (m, 1 H), 3.30-3.34 (m, 2 H), 3.88-3.92 (m, 2 H), 4.43 (d, *J*=7.42 Hz, 2 H), 7.22 (dd, *J*=9.08, 2.05 Hz, 1 H), 7.43-7.47 (m, 2 H), 7.52-7.56 (m, 1 H), 7.60 (d, *J*=2.05 Hz, 1 H), 7.75-7.80 (m, 3 H); MS (ESI) (*M*+*H*)⁺ = 428.0.

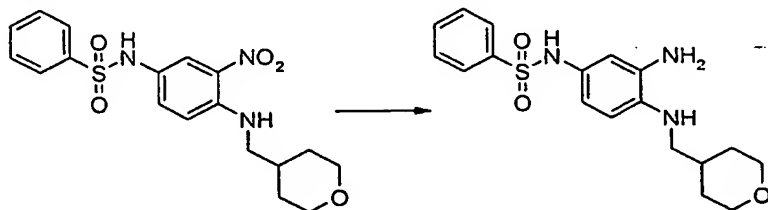
20

Step B. *N*-[3-nitro-4-[(tetrahydro-2*H*-pyran-4-yl)methyl]amino]phenyl]-benzenesulfonamide



- 4-Tetrahydropyranmethylamine (468 mg, 1.2 eq) in EtOH (0.5 mL) was added to a stirring solution of *N*-(4-fluoro-3-nitrophenyl)- benzenesulfonamide (1.0 g, 3.38 mmol) and triethylamine (0.47 mL, 1 eq) in EtOH:H₂O 4:1 (15 mL) at room temperature. The solution was heated at 60°C overnight, then cooled to room temperature. The cooled solution was poured into H₂O and was extracted (3X) with EtOAc. The combined organic phases were washed with brine and dried over anhydrous Na₂SO₄. The crude product was purified by MPLC using 1:1 heptane:EtOAc to afford the title compound as a bright red solid (767.5 mg, 58%);
- ¹H NMR (400 MHz, CDCl₃) δ 1.41-1.46 (m, 2 H), 1.65-1.75 (m, 2 H), 1.90-1.98 (m, 1 H), 3.18-3.21 (m, 2 H), 3.39-3.45 (m, 2 H), 4.00-4.04 (m, 2 H), 6.61 (s, 1 H), 6.80 (d, *J*=9.18 Hz, 1 H), 7.38 (dd, *J*=9.28, 2.64 Hz, 1 H), 7.46-7.50 (m, 2 H), 7.56-7.60 (m, 1 H), 7.69 (d, *J*=2.54 Hz, 1 H), 7.73-7.75 (m, 2 H), 8.10 (m, 1 H).

- 15 **Step C. *N*-[3-amino-4-[[[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl]-benzenesulfonamide**

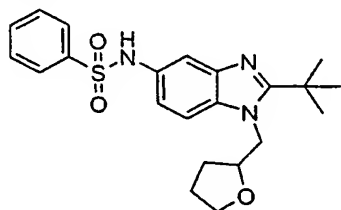


- Following the procedure for Step E in Example 3, using *N*-[3-nitro-4-[[[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl]-benzenesulfonamide (767.5 mg, 1.96 mmol) and a catalytic amount of 10% Pd/C in EtOAc (50 mL). LC/MS analysis indicated that the compound was of sufficient purity (>95%) to be used directly for Step A. Yield: 705.2 mg, 100%; ¹H NMR (400 MHz, CDCl₃) δ 1.33-1.44 (m, 2 H), 1.61-1.73 (m, 2 H), 1.81-1.88 (m, 1 H), 2.95 (d, *J*=6.64 Hz, 2 H), 3.37-3.43 (m, 5 H), 3.99 (dd, *J*=10.84, 3.42 Hz, 2 H), 6.27-6.31 (br. s., 1 H), 6.34-6.36 (m, 1 H), 6.42-6.44 (m, 1

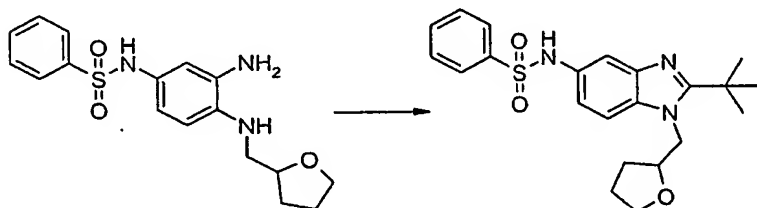
H), 6.58 (d, $J=2.34$ Hz, 1 H), 7.40-7.44 (m, 2 H), 7.50-7.55 (m, 1 H), 7.70-7.74 (m, 1 H).

Example 21

- 5 *N*-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2-furanyl)methyl]-1*H*-benzimidazol-5-yl]-benzenesulfonamide

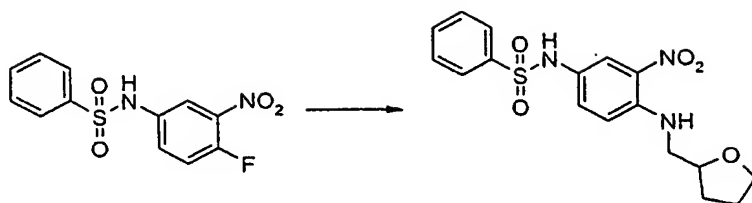


- 10 Step A. *N*-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2-furanyl)methyl]-1*H*-benzimidazol-5-yl]-benzenesulfonamide



- Following the procedure for Step A in Example 20, using *N*-[3-amino-4-[(tetrahydro-2-furanyl)methyl]amino] phenyl]-benzenesulfonamide (597.2 mg, 1.72 mmol) (for preparation, see the following steps B and C), CH_2Cl_2 (30 mL), catalytic DMAP and pivaloyl chloride (0.23 mL, 1.1 eq), followed by AcOH (3 mL), the crude product was purified by MPLC using 4:1 EtOAc:hexanes, converted to the corresponding TFA salt and lyophilized. Yield of the title product as TFA salt: 182.3 mg (17%); ^1H NMR (400 MHz, CD_3OD) δ 1.60 (s, 9 H), 1.76-1.79 (m, 1 H), 1.89-2.04 (m, 2 H), 2.18-2.26 (m, 1 H), 3.64-3.69 (m, 1 H), 3.84-3.90 (m, 1 H), 4.28-4.34 (m, 1 H), 4.53-4.59 (m, 1 H), 4.66-4.71 (m, 1 H), 7.21 (dd, $J=8.98, 1.95$ Hz, 1 H), 7.43-7.47 (m, 2 H), 7.52-7.56 (m, 1 H), 7.59 (d, $J=1.95$ Hz, 1 H), 7.75-7.79 (m, 3 H); MS (ESI) $(\text{M}+\text{H})^+ = 414.0$.

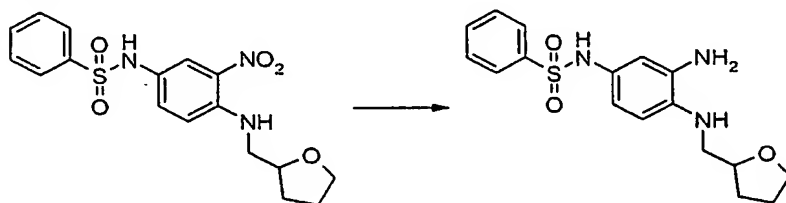
Step B. *N*-[3-nitro-4-[(tetrahydro-2-furanyl)methyl]amino]phenyl]-benzenesulfonamide



Following the procedure for Step Bin Example 20, using *N*-(4-fluoro-3-nitrophenyl)-benzenesulfonamide (1.0 g, 3.38 mmol), tetrahydrofurylamine (0.42 mL, 1.2 eq), EtOH (12 mL) and H₂O (3 mL), the crude product was purified by MPLC using 1:1
 5 heptane:EtOAc to afford the title compound as a bright red solid (749.7 mg, 59%); ¹H NMR (400 MHz, CDCl₃) δ 1.62-1.73 (m, 1 H), 1.94-2.13 (m, 3 H), 3.27-3.47 (m, 2 H), 3.80-3.98 (m, 2 H), 4.15-4.22 (m, 1 H), 6.51 (s, 1 H), 6.81 (d, *J*=9.18 Hz, 1 H), 7.35 (dd, *J*=8.98, 2.54 Hz, 1 H), 7.44-7.48 (m, 2 H), 7.55-7.59 (m, 1 H), 7.63 (d, *J*=2.73 Hz, 1 H), 7.69-7.72 (m, 2 H), 8.18-8.20 (m, 1 H).

10

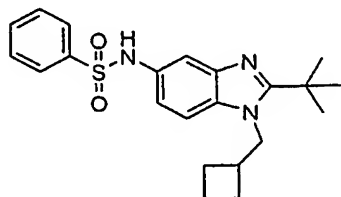
Step C. *N*-[3-amino-4-[[tetrahydro-2-furanyl)methyl]amino]phenyl]-benzenesulfonamide



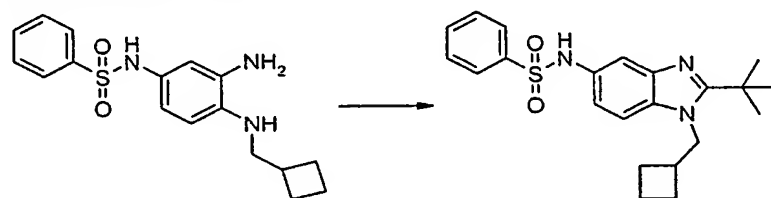
Following the procedure for Step E in Example 3, using *N*-[3-nitro-4-[[tetrahydro-2-furanyl)methyl]amino] phenyl]-benzenesulfonamide (749.7 mg, 2 mmol) and a
 15 catalytic amount of 10% Pd/C in EtOAc (50 mL), LC/MS analysis indicated that the title compound was of sufficient purity (>95%) to be used directly for the next step. Yield: 597.2 mg, 86%; ¹H NMR (400 MHz, CDCl₃) δ 1.61-1.70 (m, 2 H), 1.89-1.96 (m, 2 H), 2.01-2.09 (m, 1 H), 2.97-3.02 (m, 1 H), 3.12-3.16 (m, 1 H), 3.34-3.59 (m, 3 H), 3.74-3.90 (m, 2 H), 6.28 (s, 1 H), 6.33 (dd, *J*=8.20, 2.34 Hz, 1 H), 6.44 (d, *J*=8.40 Hz, 1 H), 6.53 (d, *J*=2.34 Hz, 1 H), 7.39-7.44 (m, 2 H), 7.50-7.54 (m, 1 H), 7.68-7.72 (m, 2 H).
 20

Example 22

***N*-[1-(cyclobutylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide**

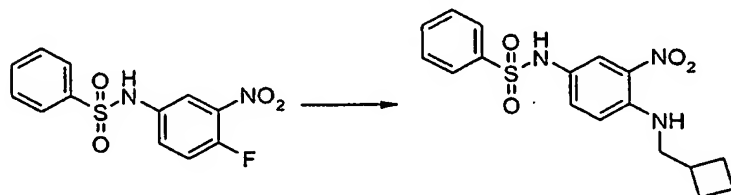


5 **Step A. *N*-[1-(cyclobutylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide**



Following the procedure for Step A in Example 20, using *N*-[3-amino-4-
 [(cyclobutylmethyl)amino]phenyl]-benzenesulfonamide (763.8 mg, 2.30 mmol) (for
 preparation, see the following steps B and C), CH₂Cl₂ (40 mL), catalytic DMAP and
 10 pivaloyl chloride (0.31 mL, 1.1 eq), followed by AcOH (9 mL), the crude product was
 purified by MPLC using 1:1 hexanes:EtOAc, followed by reversed-phase HPLC
 using 20-65% MeCN in H₂O. The compound was lyophilized to afford the title
 compound as its TFA salt (226.8 mg, 19%); ¹H NMR (400 MHz, CD₃OD) δ 1.60 (s, 9
 H), 1.81-1.93 (m, 2 H), 2.01-2.07 (m, 4 H), 2.78-2.83 (m, 1 H), 4.55 (d, *J*=6.44 Hz, 2
 15 H), 7.22 (dd, *J*=8.98, 1.95 Hz, 1 H), 7.43-7.47 (m, 2 H), 7.52-7.56 (m, 1 H), 7.59 (dd,
J=1.95, 0.59 Hz, 1 H), 7.70 (dd, *J*=8.98, 0.59 Hz, 1 H), 7.76-7.79 (m, 2 H); MS (ESI)
 (M+H)⁺ = 398.0.

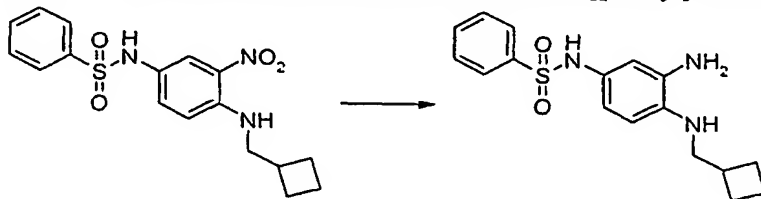
Step B. *N*-[4-[(cyclobutylmethyl)amino]-3-nitrophenyl]-benzenesulfonamide



20

Following the procedure for Step B in Example 20, using *N*-(4-fluoro-3-nitrophenyl)-benzenesulfonamide (1.0 g, 3.38 mmol), cyclobutylmethylamine (345.7 mg, 1.2 eq), EtOH (12 mL) and H₂O (5 mL) The crude product was purified by MPLC using 7:3 hexanes:EtOAc to afford the title compound as a bright orange solid (857.7 mg, 70%); ¹H NMR (400 MHz, CDCl₃) δ 1.73-1.78 (m, 2 H), 1.88-2.00 (m, 2 H), 2.13-2.21 (m, 2 H), 2.62-2.73 (m, 1 H), 3.27-3.30 (m, 2 H), 6.44 (s, 1 H), 6.78 (d, *J*=9.18 Hz, 1 H), 7.36 (dd, *J*=9.08, 2.44 Hz, 1 H), 7.45-7.49 (m, 2 H), 7.55-7.60 (m, 1 H), 7.66 (d, *J*=2.73 Hz, 1 H) 7.72-7.74 (m, 2 H), 7.93-7.98 (br s, 1 H).

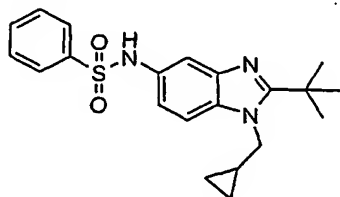
10 Step C. *N*-[3-amino-4-[(cyclobutylmethyl)amino]phenyl]-benzenesulfonamide



Following the procedure for Step E in Example 3, using *N*-[4-[(cyclobutylmethyl)amino]-3-nitrophenyl]-benzenesulfonamide (857.7 mg, 2.37 mmol) and a catalytic amount of 10% Pd/C in EtOAc (25 mL) and shaking for 48 h, LC/MS analysis indicated that the title compound was of sufficient purity (>95%) to be used directly for the next step. Yield: 763.8 mg, 97%; ¹H NMR (400 MHz, CDCl₃) δ 1.68-1.78 (m, 2 H), 1.86-1.98 (m, 2 H), 2.08-2.16 (m, 2 H), 2.54-2.62 (m, 1 H), 3.04 (d, *J*=7.42 Hz, 2 H), 3.11-3.42 (brs, 2 H), 6.28-3.31 (br. s., 1 H), 6.33 (dd, *J*=8.40, 2.34 Hz, 1 H), 6.43 (d, *J*=8.40 Hz, 1 H), 6.56 (d, *J*=2.34 Hz, 1 H), 7.40-7.44 (m, 2 H), 7.50-7.54 (m, 1 H), 7.69-7.71 (m, 2 H).

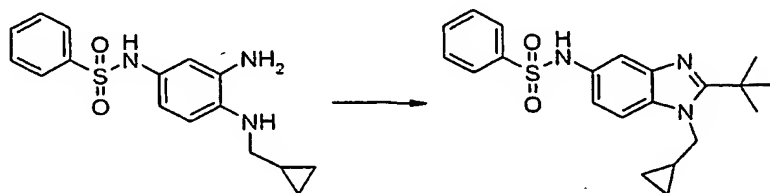
Example 23

N-[1-(cyclopropylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide



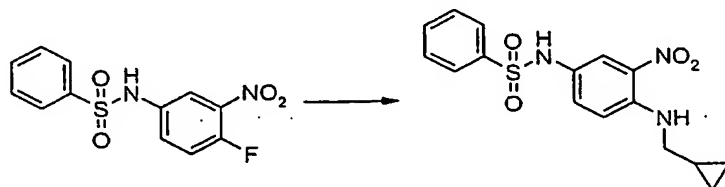
25

Step A. *N*-[1-(cyclopropylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide



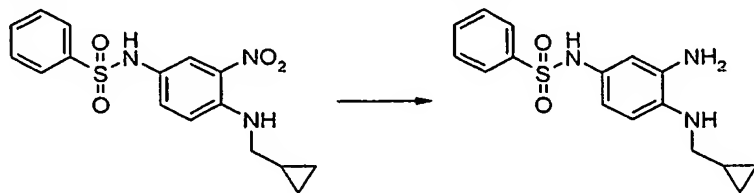
Following the procedure for Step A in Example 20, using *N*-[3-amino-4-
 5 [(cyclopropylmethyl)amino]phenyl]-benzenesulfonamide (736.4 mg, 2.32 mmol) (for
 preparation, see the following steps B and C), CH₂Cl₂ (50 mL), catalytic DMAP and
 pivaloyl chloride (0.31 mL, 1.1 eq), followed by AcOH (10 mL), the crude product
 was purified by reversed-phase HPLC using 15-45% MeCN in H₂O. The compound
 was lyophilized to afford the title compound as its TFA salt (50 mg, 4.2%); ¹H NMR
 10 (400 MHz, CD₃OD) δ 0.57-0.61 (m, 2 H), 0.65-0.70 (m, 2 H), 1.22-1.25 (m, 1 H),
 1.62 (s, 9 H), 4.47 (d, *J*=6.44 Hz, 2 H), 7.23 (dd, *J*=9.08, 2.05 Hz, 1 H), 7.43-7.47 (m,
 2 H), 7.52-7.55 (m, 1 H), 7.62 (d, *J*=1.95 Hz, 1 H), 7.74 (d, *J*=8.98 Hz, 1 H), 7.73-
 7.78 (m, 2 H); MS (ESI) (*M*+H)⁺ = 384.0.

15 Step B. *N*-[4-[(cyclopropylmethyl)amino]-3-nitrophenyl]-benzenesulfonamide



Following the procedure for Step B in Example 20, using *N*-(4-fluoro-3-nitrophenyl)-
 benzenesulfonamide (1.0 g, 3.38 mmol) and cyclopropylmethylamine (0.4 mL, 1.2
 eq) in EtOH (12 mL) and H₂O (5 mL). The crude product was purified by MPLC
 20 using 7:3 hexanes:EtOAc to afford the title compound as a bright orange solid (828.3
 mg, 71%); ¹H NMR (400 MHz, CDCl₃) δ 0.29-0.33 (m, 2 H), 0.63-0.67 (m, 2 H),
 1.14-1.19 (m, 1 H), 3.13 (dd, *J*=7.03, 4.88 Hz, 2 H), 6.42 (s, 1 H), 6.76 (d, *J*=9.37 Hz,
 1 H), 7.36 (dd, *J*=9.18, 2.54 Hz, 1 H), 7.45-7.49 (m, 2 H), 7.56-7.59 (m, 1 H), 7.67 (d,
J=2.54 Hz, 1 H), 7.71-7.74 (m, 2 H), 8.07-8.13 (m, 1 H).

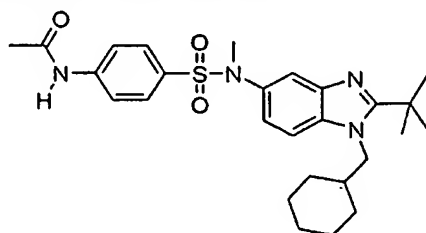
25

Step C. *N*-[3-amino-4-[(cyclopropylmethyl)amino]phenyl]-benzenesulfonamide

Following the procedure for Step E in Example 3, using *N*-[4-[(cyclopropylmethyl)amino]-3-nitrophenyl]-benzenesulfonamide (828.3 mg, 2.38 mmol), a catalytic amount of 10% Pd/C in EtOAc (30 mL). LC/MS analysis indicated that the title compound was of sufficient purity (>95%) to be used directly for the next step. Yield: 736.4 mg, 100%; ¹H NMR (400 MHz, CDCl₃) δ 0.20-0.24 (m, 2 H), 0.53-0.58 (m, 2 H), 1.08-1.12 (m, 1 H), 2.87 (d, *J*=7.03 Hz, 2 H), 3.28-3.48 (br. s., 2 H), 6.27-6.31 (br. s., 1 H), 6.31-6.34 (m, 1 H), 6.39-6.41 (m, 1 H), 6.57 (d, *J*=2.34 Hz, 1 H), 7.40-7.44 (m, 2 H), 7.49-7.54 (m, 1 H), 7.69-7.71 (m, 2 H).

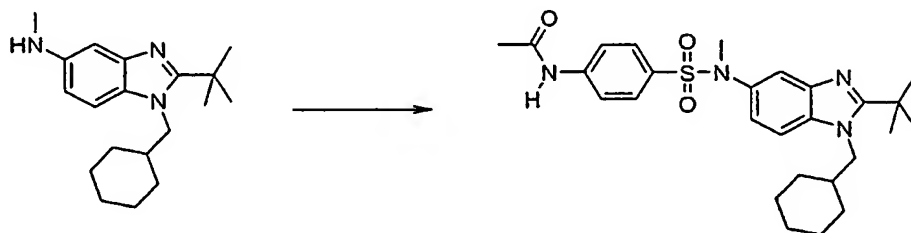
Example 24

N-(4-[[[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl) acetamide



15

Step A. *N*-(4-[[[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl) acetamide



2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (40 mg, 0.133 mmol) (for preparation, see the following steps B, C, D, E and F) and 4-acetamidobenzene sulfonyl chloride (37 mg, 0.160 mmol) were stirred in 3 mL of dichloromethane containing a catalytic amount of DMAP overnight at rt. The solvent was evaporated. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 63 mg (78%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.21 (m, 5 H), 1.61 (m, 3 H), 1.64 (s, 9 H), 1.67 (m, 1 H), 1.75 (m, 2 H), 2.07 (m, 1 H), 2.11 (s, 3 H), 3.22 (s, 3 H), 4.42 (d, *J*=7.62 Hz, 2 H), 7.29 (dd, *J*=9.08, 2.05 Hz, 1 H), 7.42 (d, *J*=8.98 Hz, 2 H), 7.50 (d, *J*=1.56 Hz, 1 H), 7.68 (d, *J*=8.98 Hz, 2 H), 7.82 (d, *J*=8.98 Hz, 1 H); MS (ESI) (*M*+*H*)⁺ 497.2; Anal. Calcd for C₂₇H₃₆N₄O₃S + 1.4 TFA + 0.4 H₂O: C, 53.94; H, 5.80; N, 8.44. Found: C, 53.98; H, 5.79; N, 8.50.

Step B. Methyl (4-fluoro-3-nitrophenyl)carbamate

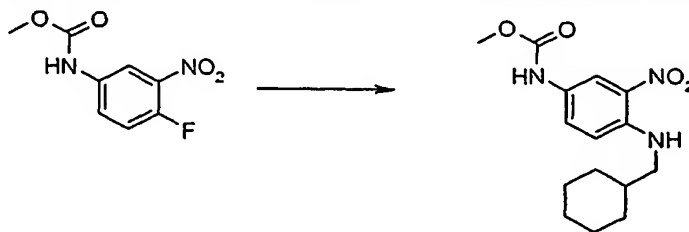


15

Methyl chloroformate (13.2 mL, 170.2 mmol) was added dropwise to a cold (0°C) dichloromethane (200 mL) solution of 4-fluoro-3-nitro aniline (24.15 g, 154.7 mmol) and DIPEA (35 mL, 201 mmol). The reaction mixture was stirred at rt overnight. The solution was then diluted with 200 mL of dichloromethane and washed with 2M HCl, brine and dried over anhydrous MgSO₄. The solvent was concentrated and the product was directly used for next step without further purification. Yield: 35.5 g (99%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 3.81 (s, 3 H), 7.02 (s, 1 H), 7.23 (m, 1 H), 7.72 (d, *J*=8.59 Hz, 1 H), 8.17 (dd, *J*=6.35, 2.64 Hz, 1 H).

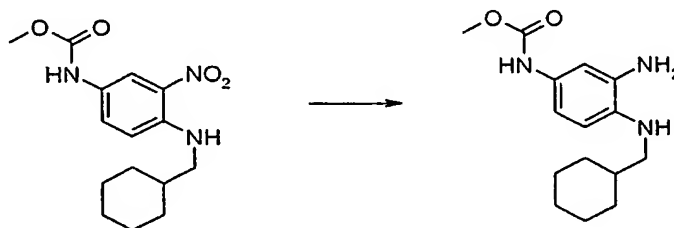
20

25 Step C. Methyl {4-[(cyclohexylmethyl)amino]-3-nitrophenyl}carbamate



Methyl (4-fluoro-3-nitrophenyl)carbamate (1.00 g, 4.67 mmol) and cyclohexylmethyl amine (0.730 mL, 5.60 mmol) were stirred in EtOH (20 mL) containing TEA (1.0 mL, 7.00 mmol) at 75°C for 24h. The solvent was concentrated. The residue was dissolved in EtOAc and washed with 5% KHSO₄ solution, saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography using 4:1/hex:EtOAc on silica gel. Yield: 1.05 g (73%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.04 (ddd, J = 24.02, 12.11, 2.93 Hz, 2H), 1.25 (m, 3H), 1.69 (m, 2H), 1.76 (m, 1H), 1.79 (m, 1H), 1.83 (m, 1H), 1.86 (m, 1H), 3.14 (dd, J = 6.44, 5.66 Hz, 2H), 3.78 (s, 3H), 6.46 (m, 1H), 6.84 (d, J = 9.37 Hz, 1H), 7.63 (m, 1H), 8.05 (d, J = 2.54 Hz, 1H), 8.09 (m, 1H).

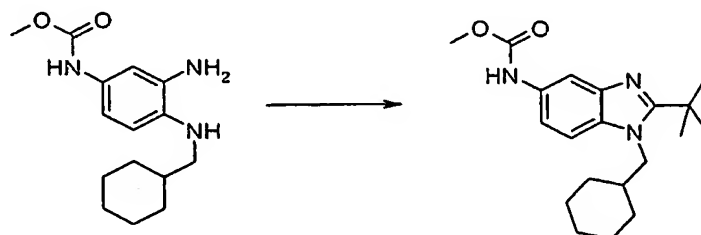
Step D. Methyl {3-amino-4-[(cyclohexylmethyl)amino]phenyl}carbamate



Methyl {4-[(cyclohexylmethyl)amino]-3-nitrophenyl}carbamate (1.05 g, 3.42 mmol) was dissolved in 30 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken in a Parr hydrogenation apparatus under H₂ atmosphere (40 psi) at rt overnight. The solution was filtered through Celite and the solvent was evaporated. The product was directly used for the next step without further purification. Yield: 950 mg (99%); MS (ESI) (M+H)⁺ 277.9.

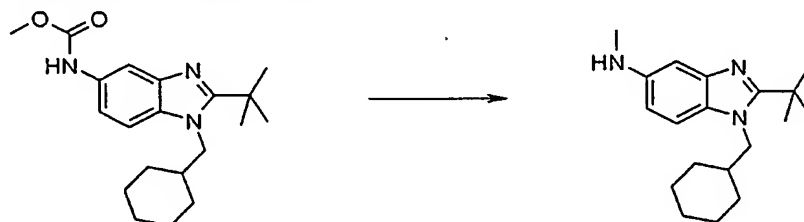
20

Step E. Methyl [2-tert-butyl-1-(cyclohexylmethyl)-1H-benzimidazol-5-yl]carbamate



Methyl {3-amino-4-[(cyclohexylmethyl)amino]phenyl}carbamate (950 mg, 3.43 mmol) and DMAP (100 mg, 0.858 mmol) were dissolved in 25 mL of dichloromethane. Trimethylacetyl chloride (0.460 mL, 3.77 mmol) was added dropwise and the solution was stirred at rt for 1h. The solvent was concentrated. The residue was divided in two portions and each of them dissolved in 3 mL of glacial AcOH in a sealed tube. The solutions were heated at 150°C using a Personal Chemistry Smith Synthesizer microwave instrument for three intervals of 30 min (3 X 30 min). The two tubes were combined and the solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography using 3:1/dichloromethane:diethyl ether. Yield: 656 mg (56%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.08 (m, 2H), 1.18 (m, 3H), 1.54 (s, 9H), 1.65 (m, 1H), 1.69 (m, 2H), 1.73 (dd, J = 5.96, 3.22 Hz, 2H), 2.02 (m, 1H), 3.78 (s, 3H), 4.10 (d, J = 7.42 Hz, 2H), 6.64 (m, 1H), 7.25 (d, J = 8.79 Hz, 1H), 7.39 (m, 1H), 7.59 (d, J = 1.76 Hz, 1H).

Step F. 2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine

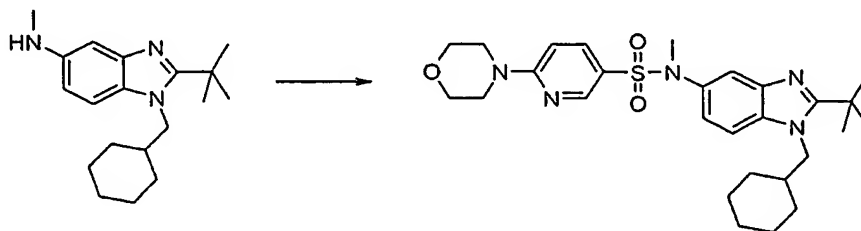


Methyl [2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbamate (650 mg, 1.89 mmol) was dissolved in 20 mL of THF at 0°C under nitrogen. 1M HCl/ether (2.65 mL, 2.65 mmol) was added dropwise and the solution stirred at 0°C for 15min. LiAlH₄ (360 mg, 9.45 mmol) was then slowly added and the solution was stirred at rt overnight. The reaction mixture was quenched at 0°C by addition of MeOH (5 mL) followed by water (10 mL). The solution was diluted with EtOAc and washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated and the product was used directly for Step A without further purification. Yield: 544 mg (96%). ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.08 (s, 2 H) 1.17 (m, 3 H) 1.54 (s, 9 H) 1.64 (m, 2 H) 1.67 (m, 2 H) 1.72 (m, 2 H) 2.02 (m, 1 H) 2.87 (s,

3 H) 4.06 (d, $J=7.62$ Hz, 2 H) 6.60 (dd, $J=8.69, 2.25$ Hz, 1 H) 7.00 (d, $J=1.76$ Hz, 1 H) 7.12 (d, $J=8.59$ Hz, 1 H).

Example 25

5 *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-6-morpholin-4-ylpyridine-3-sulfonamide

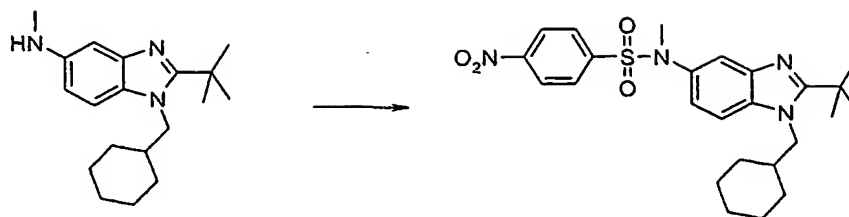


Following the procedure for Step A in Example 24, using 2-*tert*-butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (39 mg, 0.130 mmol), 6-morpholino-3-pyridinesulfonyl chloride (41 mg, 0.156 mmol) and DMAP (catalytic) in 2 mL of DCM. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 11 mg (13%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.21 (m, 5 H), 1.61 (m, 2 H), 1.64 (s, 9 H), 1.67 (m, 1 H), 1.75 (m, 2 H), 2.08 (s, 1 H), 3.23 (s, 3 H), 3.60 (m, 4 H), 3.71 (m, 4 H), 4.42 (d, $J=7.62$ Hz, 2 H), 6.77 (d, $J=8.59$ Hz, 1 H), 7.34 (dd, $J=8.98, 1.95$ Hz, 1 H), 7.57 (m, 2 H), 7.83 (d, $J=8.98$ Hz, 1 H), 8.08 (d, $J=1.95$ Hz, 1 H); MS (ESI) (M+H)⁺ 526.0; Anal. Calcd for C₂₈H₃₉N₅O₃S + 1.7 TFA + 0.5 H₂O: C, 51.77; H, 5.77; N, 9.61. Found: C, 51.76; H, 5.75; N, 9.69.

20

Example 26

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-nitrobenzenesulfonamide



Following the procedure for Step A in Example 24, using 2-*tert*-butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (253 mg, 0.845 mmol), 4-nitrobenzenesulfonyl chloride (245 mg, 1.10 mmol) and DMAP (catalytic) in 20 mL of DCM. The solution was washed with saturated NaHCO₃ aqueous solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography on silica gel using 2:1 / hexanes:EtOAc as eluent to afford the title product. Yield: 380 mg (93%); ¹H NMR (400 MHz, CHLOROFORM-*D*) δ 1.09 (m, 2 H) 1.21 (m, 3 H) 1.54 (s, 9 H) 1.64 (m, 1 H) 1.67 (m, 1 H) 1.71 (m, 1 H) 1.76 (m, 2 H) 2.03 (m, 1 H) 3.27 (s, 3 H) 4.12 (d, *J*=7.23 Hz, 2 H) 7.18 (m, *J*=8.98 Hz, 2 H) 7.30 (d, *J*=8.98 Hz, 1 H) 7.77 (d, *J*=9.18 Hz, 2 H) 8.30 (d, *J*=9.18 Hz, 2 H).

Example 27

4-Amino-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



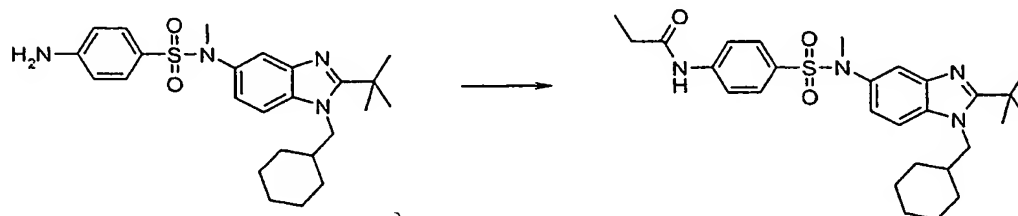
N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-nitrobenzenesulfonamide (375mg, 0.774 mmol) was dissolved in 20 mL of EtOH containing a catalytic amount of 10% Pd/C. The solution was shaken in a Parr hydrogenation apparatus under H₂ atmosphere (40 psi) at rt for 3h. The solution was filtered through celite and the solvent was concentrated. Yield: 332 mg (94%); ¹H NMR (400 MHz, METHANOL-*D*₄) δ 1.22 (m, 6 H) 1.60 (m, 1 H) 1.64 (s, 9 H) 1.67 (m, 1 H) 1.75 (m, 2 H) 2.08 (m, 1 H) 3.17 (s, 3 H) 4.42 (d, *J*=7.42 Hz, 2 H) 6.56 (d,

J=8.79 Hz, 2 H) 7.14 (d, J=8.79 Hz, 2 H) 7.32 (dd, J=8.98, 1.95 Hz, 1 H) 7.49 (d, J=1.95 Hz, 1 H) 7.81 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 455.0; Anal. Calcd for C₂₅H₃₄N₄O₂S + 1.5 TFA + 0.4 H₂O: C, 53.14; H, 5.78; N, 8.85. Found: C, 53.10; H, 5.67; N, 8.92.

5

Example 28

N-(4-{[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino)sulfonyl}phenyl)propanamide

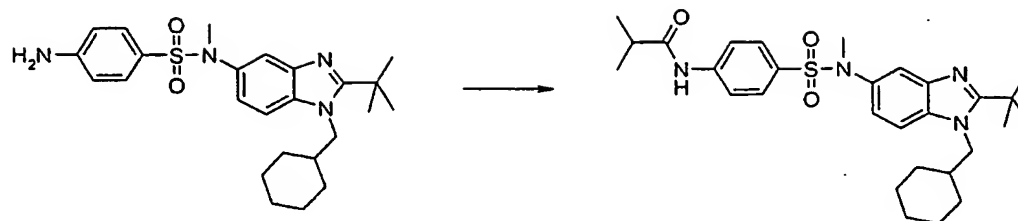


10

4-Amino-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (50 mg, 0.110 mmol) and propionyl chloride (0.012 mL, 0.143 mmol) were stirred in 3 mL of DCM containing a catalytic amount of DMAP at
 15 rt for 12h. The solvent was concentrated and the crude product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 68mg (99%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.16 (t, J=7.62 Hz, 3 H) 1.21 (m, 5 H) 1.60 (m, 2 H) 1.64 (s, 9 H) 1.67 (m, 1 H) 1.75 (m, 2 H) 2.07 (m, 1 H) 2.38 (q, J=7.62 Hz, 2 H) 3.22 (s, 3
 20 H) 4.42 (d, J=7.62 Hz, 2 H) 7.29 (dd, J=9.08, 2.05 Hz, 1 H) 7.42 (d, J=8.98 Hz, 2 H) 7.49 (d, J=1.76 Hz, 1 H) 7.69 (d, J=8.98 Hz, 2 H) 7.81 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 511.2; Anal. Calcd for C₂₈H₃₈N₄O₃S + 1.5 TFA + 0.2 H₂O: C, 54.33; H, 5.87; N, 8.18. Found: C, 54.32; H, 5.84; N, 8.25.

Example 29

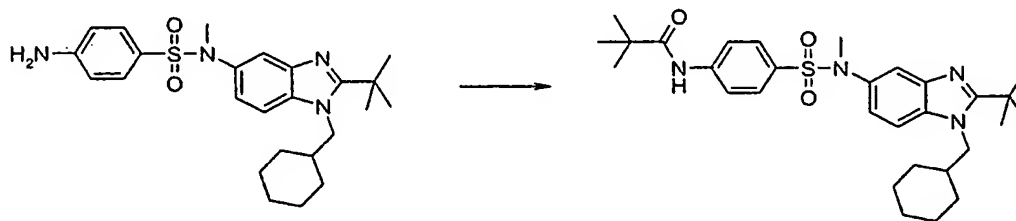
N-(4-{[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino)sulfonyl}phenyl)-2-methylpropanamide



Following the procedure for Example 28, using 4-amino-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (50 mg, 0.110 mmol), isobutyryl chloride (0.015 mL, 0.143 mmol) and a catalytic amount of DMAP in 3mL of DCM. Yield: 73mg (99%); ¹H NMR (400 MHz, METHANOL-*D*₄) δ 1.15 (d, *J*=6.83 Hz, 6 H) 1.21 (m, 5 H) 1.62 (m, 2 H) 1.64 (s, 9 H) 1.67 (m, 1 H) 1.75 (m, 2 H) 2.08 (m, 1 H) 2.61 (dt, *J*=13.82, 6.86 Hz, 1 H) 3.23 (s, 3 H) 4.42 (d, *J*=7.62 Hz, 2 H) 7.29 (dd, *J*=8.98, 1.95 Hz, 1 H) 7.42 (d, *J*=8.98 Hz, 2 H) 7.50 (d, *J*=1.95 Hz, 1 H) 7.71 (d, *J*=8.98 Hz, 2 H) 7.82 (d, *J*=8.98 Hz, 1 H); MS (ESI) (*M*+*H*)⁺ 525.3; Anal. Calcd for C₂₉H₄₀N₄O₃S + 1.7 TFA + 0.3 H₂O: C, 53.75; H, 5.89; N, 7.74. Found: C, 53.75; H, 5.87; N, 7.73.

Example 30

N-(4-[[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2,2-dimethylpropanamide

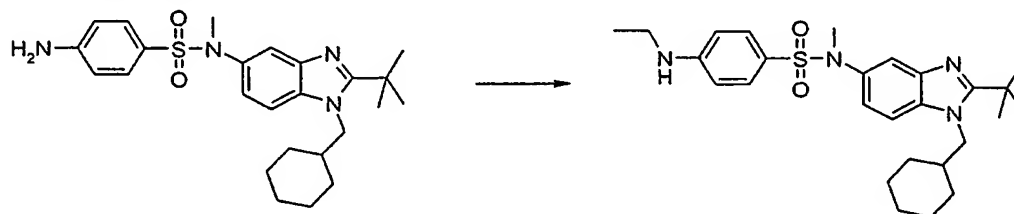


Following the procedure for Example 28, using 4-amino-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (50 mg, 0.110 mmol), trimethylacetyl chloride (0.018 mL, 0.143 mmol) and a catalytic amount of DMAP in 3mL of DCM. Yield: 76mg (99%); ¹H NMR (400 MHz, METHANOL-*D*₄) δ 1.21 (m, 5 H) 1.26 (s, 9 H) 1.62 (m, 2 H) 1.64 (s, 9 H) 1.67 (m, 1 H) 1.75 (m, 2 H) 2.07 (m, 1 H) 3.23 (s, 3 H) 4.42 (d, *J*=7.62 Hz, 2 H) 7.29 (dd, *J*=9.08, 2.05 Hz, 1 H) 7.42 (d, *J*=8.98 Hz, 2 H) 7.49 (d, *J*=1.76 Hz, 1 H) 7.73 (d,

$J=8.98$ Hz, 2 H) 7.82 (d, $J=8.98$ Hz, 1 H); MS (ESI) $(M+H)^+$ 539.2; Anal. Calcd for $C_{30}H_{42}N_4O_3S + 1.4$ TFA + 0.5 H_2O : C, 55.69; H, 6.33; N, 7.92. Found: C, 55.70; H, 6.31; N, 7.92.

5 Example 31

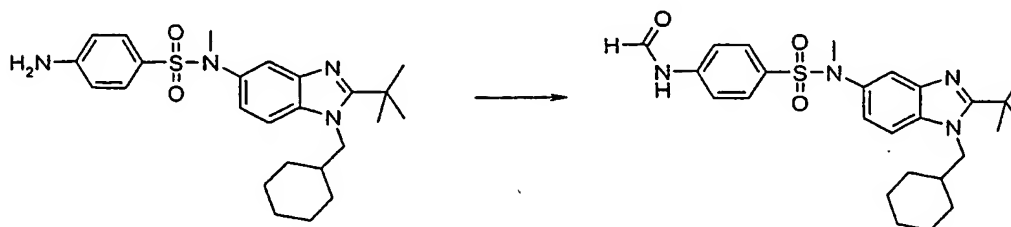
N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-4-(ethylamino)-*N*-methylbenzenesulfonamide



- 10 4-Amino-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (55 mg, 0.121 mmol), cesium carbonate (78 mg, 0.242 mmol) and ethyl iodide (0.011 mL, 0.133 mmol) were dissolved in 1 mL of DMF in a sealed tube flushed with nitrogen. The solution was heated at 125°C in a Personal Chemistry SmithSynthesizer microwave instrument for 10 min. Another 0.133 mmol (0.011 mL) of ethyl iodide was added and the solution was heated for another 10 min. This procedure was then repeated 3 more times. The solvent was then concentrated. The residue was dissolved in EtOAc and washed with saturated $NaHCO_3$ aqueous solution, brine and dried over anhydrous $MgSO_4$. The solvent was concentrated and the crude product was purified by reversed-phase HPLC using 20-80% CH_3CN/H_2O and then lyophilized affording the title compound as the corresponding TFA salt.
- 20 Yield: 39 mg (54%); 1H NMR (400 MHz, METHANOL- D_4) δ 1.19 (t, $J=7.23$ Hz, 3 H) 1.23 (m, 5 H) 1.62 (m, 2 H) 1.64 (s, 9 H) 1.67 (m, 1 H) 1.75 (m, 2 H) 2.08 (m, 1 H) 3.10 (q, $J=7.23$ Hz, 2 H) 3.17 (s, 3 H) 4.43 (d, $J=7.62$ Hz, 2 H) 6.52 (d, $J=8.98$ Hz, 2 H) 7.18 (d, $J=8.98$ Hz, 2 H) 7.32 (dd, $J=8.98$, 1.95 Hz, 1 H) 7.51 (d, $J=2.15$ Hz, 1 H) 7.81 (d, $J=8.98$ Hz, 1 H); MS (ESI) $(M+H)^+$ 483.3; Anal. Calcd for $C_{27}H_{38}N_4O_2S + 1.8$ TFA: C, 53.43; H, 5.83; N, 8.14. Found: C, 53.51; H, 5.81; N, 8.13.
- 25

Example 32

***N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-4-(formylamino)-*N*-methylbenzenesulfonamide**

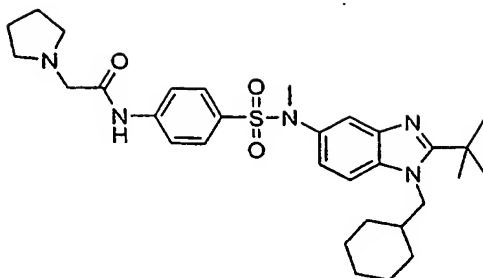


5

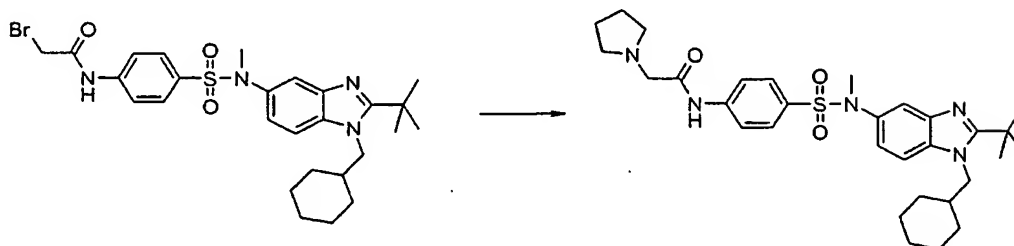
4-Amino-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (45 mg; 0.099 mmol), was heated in 1 mL of formic acid in a sealed tube at 125°C for 15 min using a Personal Chemistry SmithSynthesizer microwave instrument. The solvent was concentrated and the product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 61 mg (99%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.21 (m, 5 H), 1.62 (m, 2 H), 1.64 (s, 9 H), 1.67 (m, 1 H), 1.75 (m, 2 H), 2.08 (m, 1 H), 3.23 (s, 3 H), 4.42 (d, J=7.62 Hz, 2 H), 7.29 (dd, J=8.98, 1.95 Hz, 1 H), 7.45 (d, J=8.98 Hz, 2 H), 7.50 (d, J=1.76 Hz, 1 H), 7.70 (d, J=8.79 Hz, 2 H), 7.82 (d, J=8.98 Hz, 1 H), 8.31 (s, 1 H); MS (ESI) (M+H)⁺ 483.0; Anal. Calcd for C₂₆H₃₄N₄O₃S + 1.4 TFA + 0.5 H₂O: C, 53.11; H, 5.63; N, 8.60. Found: C, 53.02; H, 5.62; N, 8.71.

Example 33

***N*-(4-[[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl)-2-pyrrolidin-1-ylacetamide**



STEP A: *N*-(4-({[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-pyrrolidin-1-ylacetamide

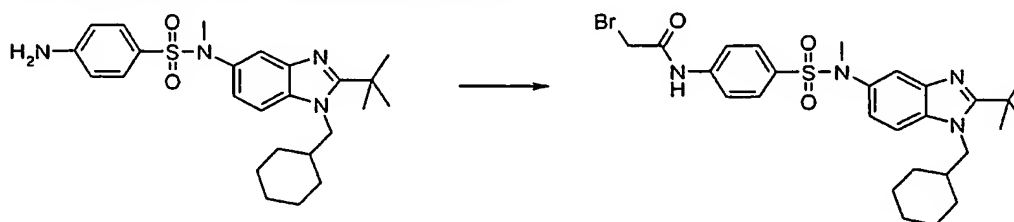


5

2-Bromo-*N*-(4-({[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide (42 mg, 0.0730 mmol) and pyrrolidine (0.030 mL, 0.365 mmol) were dissolved in 1 mL of DMF in a sealed tube. The solution was heated at 125°C in a Personal Chemistry SmithSynthesizer microwave instrument for 15 min. The solvent was concentrated. The residue was dissolved in EtOAc and was washed with saturated NaHCO₃ aqueous solution, brine and dried over anhydrous MgSO₄. The solvent was concentrated and the crude product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 51 mg (88%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.24 (m, 5 H) 1.63 (m, 2 H) 1.67 (s, 11 H) 1.70 (m, 1 H) 1.78 (m, 2 H) 2.09 (m, 2 H) 2.17 (m, 2 H) 3.19 (m, 1 H) 3.27 (s, 3 H) 3.78 (m, 1 H) 4.27 (s, 2 H) 4.44 (d, J=7.62 Hz, 2 H) 7.28 (dd, J=8.98, 1.95 Hz, 1 H) 7.53 (d, J=8.98 Hz, 2 H) 7.59 (d, J=1.76 Hz, 1 H) 7.77 (d, J=8.98 Hz, 2 H) 7.82 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 566.2; Anal. Calcd for C₃₁H₄₃N₅O₃S + 2.7 TFA + 0.4 H₂O: C, 49.63; H, 5.32; N, 7.95. Found: C, 49.63; H, 5.33; N, 7.93.

20

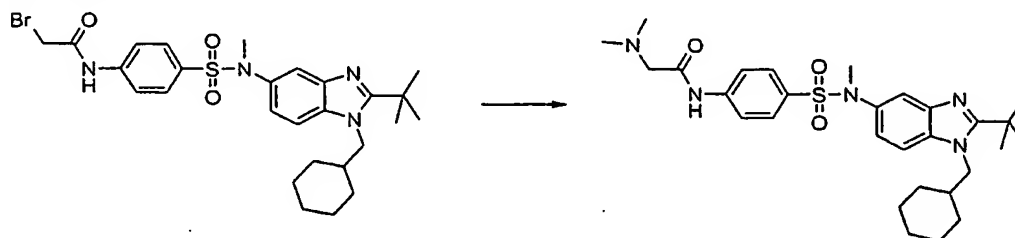
STEP B: 2-Bromo-*N*-(4-{[[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide



- 5 4-Amino-*N*-(2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl)-*N*-methylbenzenesulfonamide (155 mg, 0.341 mmol) was dissolved in 5 mL of DCM containing a catalytic amount of DMAP. Bromoacetyl chloride (0.035 mL, 0.409 mmol) was added and the solution was stirred at rt for 3h. The solution was washed with saturated NaHCO₃ aqueous solution, brine and dried over anhydrous MgSO₄.
- 10 The crude product was purified by flash chromatography on silica gel using 50-75% EtOAc in hexanes as eluent to afford the title product. Yield: 175 mg (89%); ¹H NMR (400 MHz, CHLOROFORM-*D*) δ 1.09 (m, 1H) 1.12 (m, 1H) 1.15 (m, 1H) 1.19 (d J=8.59 Hz, 2H) 1.54 (s, 9H) 1.65 (m, 1H) 1.68 (m, 1H) 1.72 (m, 1H) 1.75 (m, 2H) 2.04 (m, 1H) 3.21 (d, J=1.17 Hz, 3H) 4.04 (s, 1H) 4.12 (m, 2H) 4.22 (s, 1H) 7.20 (m,
- 15 1H) 7.23 (m, 1H) 7.28 (m, 1H) 7.57 (m, 2H) 7.66 (t, J=8.49 Hz, 2H) 8.44 (d, J=8.40 Hz, 1H).

Example 34

- N*¹-(4-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-*N*²,*N*²-dimethylglycinamide
- 20

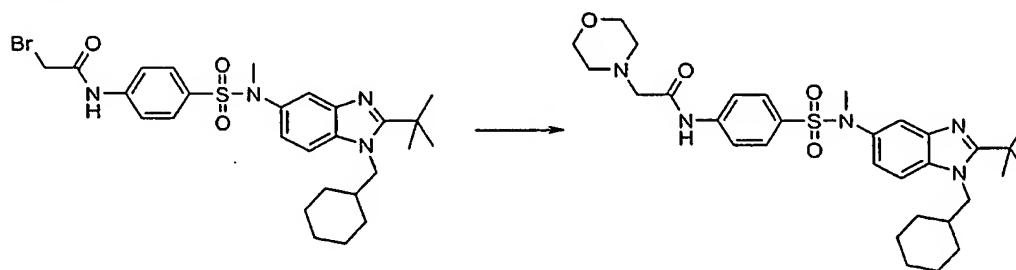


Following the procedure for Example 33, using 2-bromo-*N*-(4-{[[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)

acetamide (40 mg, 0.0695 mmol), dimethylamine hydrochloride (0.030 mg, 0.348 mmol) and DIPEA (0.060 mL, 0.348 mmol) in 1 mL of DMF. Yield: 35 mg (77%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.24 (m, 5 H) 1.64 (m, 2 H) 1.67 (s, 9 H) 1.70 (m, 1 H) 1.78 (m, 2 H) 2.10 (m, 1 H) 3.00 (s, 6 H) 3.27 (s, 3 H) 4.18 (s, 2 H) 4.45 (d, J=7.62 Hz, 2 H) 7.29 (dd, J=8.98, 1.95 Hz, 1 H) 7.54 (d, J=8.98 Hz, 2 H) 7.60 (d, J=1.76 Hz, 1 H) 7.77 (d, J=8.98 Hz, 2 H) 7.82 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 540.3; Anal. Calcd for C₂₉H₄₁N₅O₃S + 2.9 TFA + 0.5 H₂O: C, 47.53; H, 5.15; N, 7.96. Found: C, 47.57; H, 5.11; N, 7.99.

10 Example 35

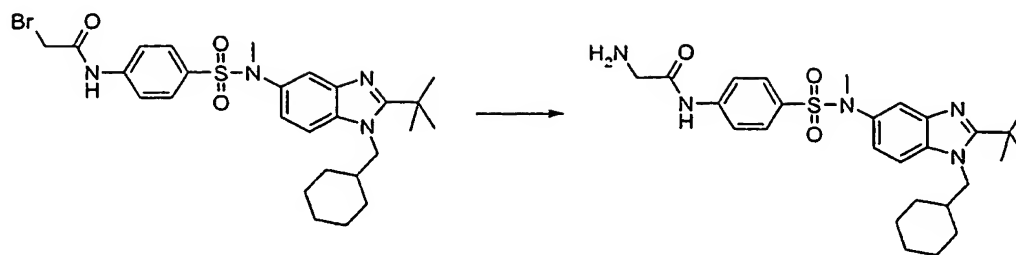
N-(4-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-morpholin-4-ylacetamide



- 15 Following the procedure for Example 33, using 2-bromo-*N*-(4-{[[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-acetamide (56 mg, 0.0973 mmol) and morpholine (0.045 mL, 0.486 mmol) in 1 mL of DMF. Yield: 15mg (26%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.24 (m, 5 H) 1.64 (m, 2 H) 1.67 (s, 9 H) 1.70 (m, 1 H) 1.78 (m, 2 H) 2.11 (m, 1 H) 3.27 (s, 3 H) 3.42 (m, 4 H) 3.96 (m, 4 H) 4.17 (s, 2 H) 4.45 (d, J=7.62 Hz, 2 H) 7.29 (dd, J=8.98, 2.15 Hz, 1 H) 7.54 (d, J=9.18 Hz, 2 H) 7.60 (d, J=1.56 Hz, 1 H) 7.77 (d, J=8.98 Hz, 2 H) 7.83 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 582.2; Anal. Calcd for C₃₁H₄₃N₅O₄S + 3.2 TFA + 0.2 H₂O: C, 47.27; H, 4.94; N, 7.37. Found: C, 47.23; H, 4.92; N, 7.49.

25 Example 36

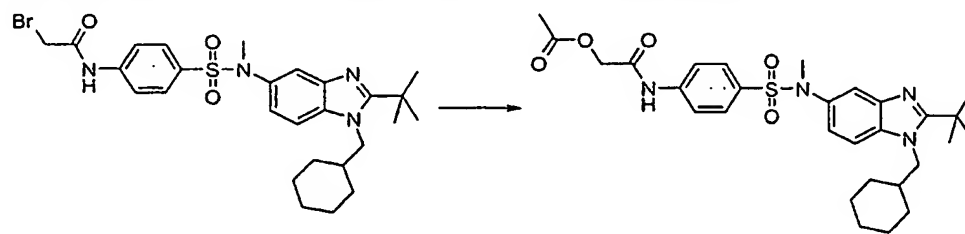
*N*¹-(4-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)glycinamide



Following the procedure for Example 33, using 2-bromo-*N*-(4-([2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino)sulfonyl)phenyl)acetamide (37 mg, 0.0608 mmol) and ammonium hydroxide (28% aqueous) (0.5 mL, excess) in 1 mL of DMF. Yield: 28mg (74%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.24 (m, 5 H), 1.64 (m, 2 H), 1.67 (s, 9 H), 1.70 (m, 1 H), 1.78 (m, 2 H), 2.10 (m, 1 H), 3.27 (s, 3 H), 3.89 (s, 2 H), 4.44 (d, J=7.62 Hz, 2 H), 7.30 (dd, J=8.98, 1.95 Hz, 1 H), 7.53 (d, J=9.18 Hz, 2 H), 7.58 (d, J=1.76 Hz, 1 H), 7.76 (d, J=8.98 Hz, 2 H), 7.82 (d, J=9.18 Hz, 1 H); MS (ESI) (M+H)⁺ 512.0; Anal. Calcd for C₂₇H₃₇N₅O₃S + 2.6 TFA + 1.6 H₂O: C, 46.21; H, 5.15; N, 8.37. Found: C, 46.22; H, 5.09; N, 8.43.

Example 37

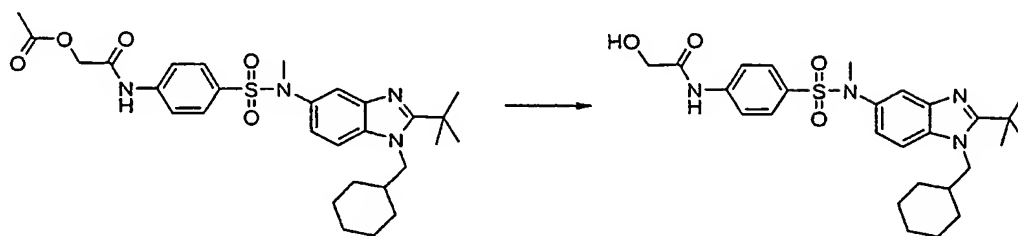
2-[(4-([2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino)sulfonyl)phenyl]amino]-2-oxoethyl acetate



Following the procedure for Example 33, using 2-bromo-*N*-(4-([2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino)sulfonyl)phenyl)acetamide (50 mg, 0.0869 mmol) and sodium acetate (35 mg, 0.434 mmol) in 2 mL of DMF. The product was used directly for the next step without any further purification. Yield: 48 mg (99%); MS (ESI) (M+H)⁺ 555.2.

Example 38

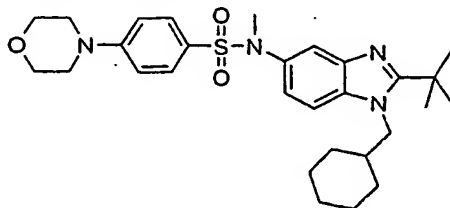
***N*-(4-[[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl)-2-hydroxyacetamide**



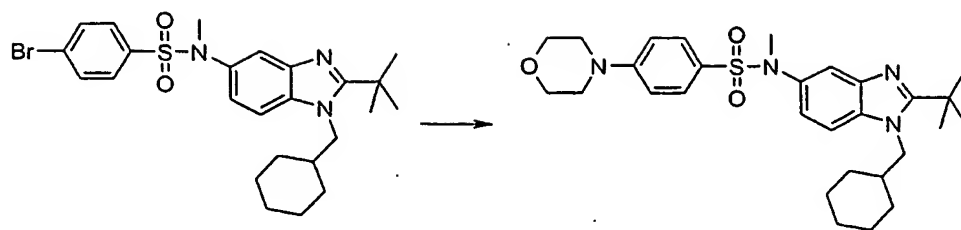
- 5 2-[(4-[[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl)amino]-2-oxoethyl acetate (48 mg, 0.0869 mmol) was refluxed in 2 mL of EtOH containing 1M LiOH (0.5 mL, excess) for 2h. The solvent was concentrated and the residue was dissolved in EtOAc. The organic phase was washed with saturated NaHCO₃ aqueous solution, brine and dried over anhydrous
- 10 MgSO₄. The solvent was concentrated and the crude product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 16 mg (29%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.24 (m, 5 H), 1.63 (m, 2 H), 1.67 (s, 9 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 2.10 (m, 1 H), 3.27 (s, 3 H), 4.13 (s, 2 H), 4.45 (d, J=7.62 Hz, 2 H),
- 15 7.31 (dd, J=9.08, 2.05 Hz, 1 H), 7.49 (d, J=8.79 Hz, 2 H), 7.53 (d, J=1.95 Hz, 1 H), 7.83 (m, 3 H); MS (ESI) (M+H)⁺ 513.0.

Example 39

- N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(4-morpholinyl)-benzenesulfonamide**
- 20

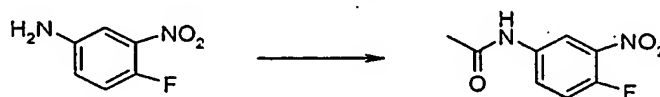


Step A. *N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(4-morpholinyl)-benzenesulfonamide



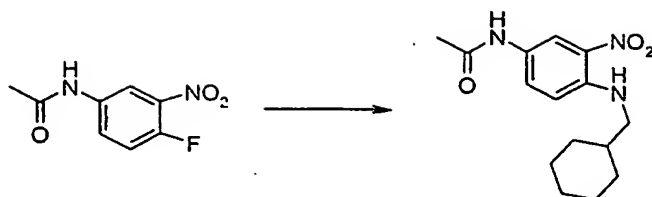
4-Bromo-*N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzenesulfonamide (for preparation, see the following steps B, C, D, E, F, G and H) (80.1 mg, 0.154 mmol), morpholine (16 μ L, 15.7 mg, 0.18 mmol), KO^tBu-t (20.2 mg, 0.21 mmol), Pd(dba)₂ (12.9 mg, 0.014 mmol) and BINAP (11.5 mg, 0.018 mmol) in toluene (3 mL) were placed in a sealed tube. The mixture was heated at 170°C in a Personal Chemistry SmithSynthesizer microwave instrument for 30 min, diluted with EtOAc (50 mL), brine (2x10 mL) and dried over anhydrous Na₂SO₄. The solvent was concentrated and the crude product was purified by reversed-phase HPLC using 20-70% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA. Yield: 45.3 mg (46%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.25 (m, 5 H), 1.63 (m, 2 H), 1.67 (s, 9 H), 1.72 (m, 1 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 3.23 (s, 3 H), 3.28 (m, 4 H), 3.80 (m, 4 H), 4.45 (d, *J*=7.62 Hz, 2 H), 6.96 (m, 2 H), 7.33 (dd, *J*=9.08, 2.05 Hz, 1 H), 7.37 (m, 2 H), 7.54 (d, *J*=1.76 Hz, 1 H), 7.84 (d, *J*=8.98 Hz, 1 H); MS (ESI) (*M*+H)⁺ 525.3.

Step B. *N*-(4-fluoro-3-nitrophenyl)acetamide



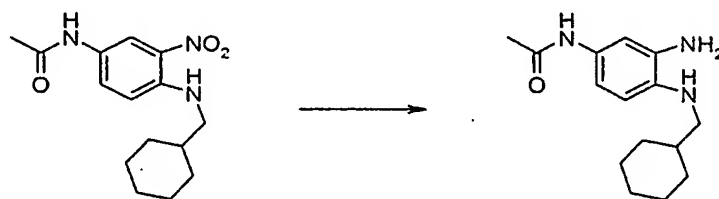
4-Fluoro-3-nitro-aniline (45.0 g, 0.288 mol) was added portionwise to acetic anhydride (150 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The white solid was collected and dried *in vacuo* to give the title compound (42.0 g, 70%). ¹H NMR (400 MHz, CDCl₃): δ 2.23 (s, 3 H), 7.26 (m, 1 H), 7.50 (s broad, 1 H), 7.87 (m, 1 H), 8.23 (dd, *J*=6.44, 2.73 Hz, 1 H).

Step C. *N*-{4-[(cyclohexylmethyl)amino]-3-nitrophenyl}acetamide



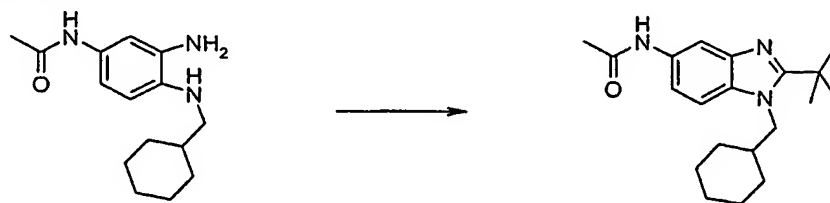
Cyclohexylmethylamine (2.86 mL, 2.49 g, 22.0 mmol) was added to a mixture of *N*-(4-fluoro-3-nitrophenyl)acetamide (3.96 g, 20.0 mmol) and sodium carbonate (4.66 g, 44 mmol) in EtOH (50 mL) at room temperature. The reaction mixture was heated for 48 h at 60 °C, and diluted with H₂O (800 mL). The orange solid was precipitated out and collected to give the title product (6.60 g, 100%). MS (ESI) (M+H)⁺: 292.3.

Step D. *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}acetamide



N-(4-[(Cyclohexylmethyl)amino]-3-nitrophenyl)acetamide was hydrogenated in ethyl acetate (300 mL) catalyzed by 10% Pd/C (0.5 g) at 20-30 psi H₂ in Parr shaker for 4.5 h at room temperature. After filtration through celite and concentration, 5.08 g (97%) of a purple solid was obtained, which was used in the next step without purification. ¹H NMR (400 MHz, CDCl₃): δ 1.00 (m, 2 H), 1.24 (m, 3 H), 1.59 (m, 2 H), 1.72 (m, 2 H), 1.84 (m, 2 H), 2.13 (s, 3 H), 2.91 (d, *J*=6.64 Hz, 2 H), 3.37 (s broad, 3 H), 6.56 (d, *J*=8.40 Hz, 1 H), 6.69 (dd, *J*=8.30, 2.25 Hz, 1 H), 6.98 (s, 1 H), 7.12 (d, *J*=2.34 Hz, 1 H); MS (ESI) (M+H)⁺: 262.3.

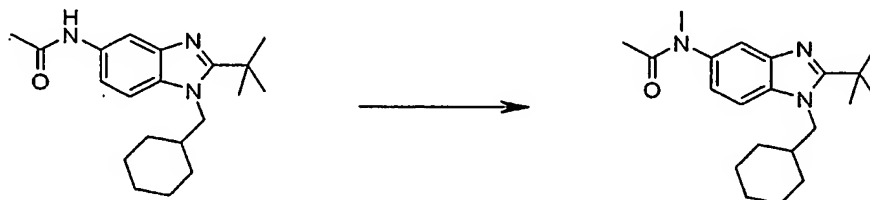
Step E. *N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]acetamide



DMAP (0.15 g, 1.2 mmol) was added to a solution of *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl} acetamide (1.57 g, 6.0 mmol) in dichloromethane (70 mL) at 0 °C, followed by addition of trimethylacetyl chloride (0.85 mL, 0.83 g, 6.6 mmol). The resulting mixture was stirred overnight at room temperature. After
5 evaporation of the solvent, the residue was dissolved in dichloroethane (40 mL) and then divided to 8 sealed test tubes. The mixture was heated at 170°C in a Personal Chemistry SmithSynthesizer microwave instrument for 2 h. The combined reaction mixture was dissolved in EtOAc (200 mL), washed with 2N NaOH aqueous solution (2x10 mL), brine (2x10 mL) and dried over Na₂SO₄. After filtration and evaporation,
10 the residue was purified by MPLC using EtOAc as eluent on silica gel to give the title compound as a white solid (1.42 g, 72%). ¹H NMR (400 MHz, METHANOL-D₄) δ 1.24 (m, 5 H), 1.64 (m, 2 H), 1.67 (s, 9 H), 1.70 (m, 1 H), 1.77 (m, 2 H), 2.12 (m, 1 H), 2.18 (s, 3 H), 4.45 (d, J=7.62 Hz, 2 H), 7.50 (m, 1 H), 7.84 (d, J=8.98 Hz, 1 H), 8.43 (d, J=1.95 Hz, 1 H); MS (ESI) (M+H)⁺: 328.2.

15

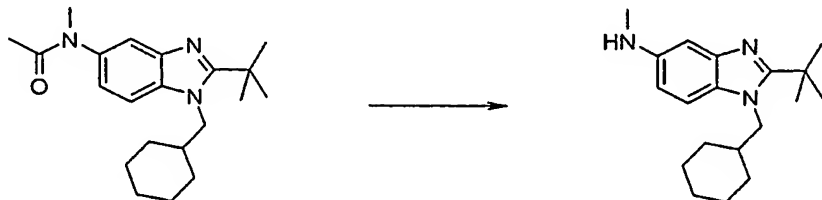
Step F. *N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-acetamide



Sodium hydride (60%, 201.5 mg, 5.04 mmol) was added to a solution of *N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]acetamide (549.8
20 mg, 1.68 mmol) in THF (50 mL) at 0 °C. Stirring for 1h, MeI (0.31 mL, 715.4 mg, 5.04 mmol) was added. The mixture was stirred overnight at room temperature, quenched with saturated NaHCO₃ (5 mL), and extracted with EtOAc (3x20 mL). The combined organic phases were washed with saturated. NaHCO₃ (20 mL), brine (20
25 mL) and dried over Na₂SO₄. After filtration and concentration, the residue was purified by MPLC using EtOAc to give 580.5 mg (100%) of the title compound as a white solid. ¹H NMR (400 MHz, METHANOL-D₄) δ 1.26 (m, 5 H), 1.67 (m, 2 H), 1.69 (s, 9 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 1.87 (s, 3 H), 2.14 (m, 1 H), 3.30 (s, 3 H),

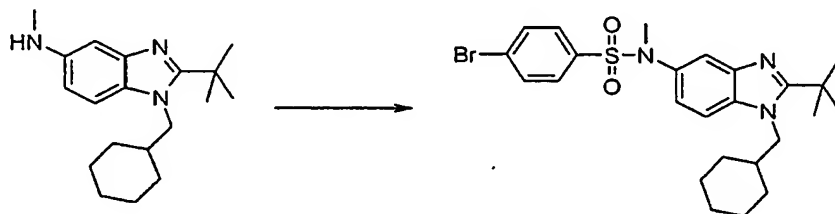
4.49 (d, $J=7.62$ Hz, 2 H), 7.55 (d, $J=8.40$ Hz, 1 H), 7.71 (s, 1 H), 8.00 (d, $J=8.40$ Hz, 1 H); MS (ESI) (M+H)⁺ 342.2.

Step G. *N*-1-(Cyclohexylmethyl)-2-(1,1-dimethylethyl)-*N*-methyl-1*H*-benzimidazol-5-amine



N-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]acetamide (540.6 mg, 1.58 mmol) was dissolved in 20 mL of EtOH-2*N* HCl (3:2), and then heated at 120°C in a Personal Chemistry SmithSynthesizer microwave instrument for 30 min. After concentration and dried in vacuum, 603.5 mg (100%) of a white solid was obtained as the title product. ¹H NMR (400 MHz, METHANOL-D₄) δ 1.26 (m, 5 H), 1.65 (m, 3 H), 1.71 (s, 9 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 3.17 (s, 3 H), 4.53 (d, $J=7.62$ Hz, 2 H), 7.75 (m, 1 H), 8.03 (m, 1 H), 8.17 (m, 1 H); MS (ESI) (M+H)⁺ 300.1.

Step H. 4-Bromo-*N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzenesulfonamide

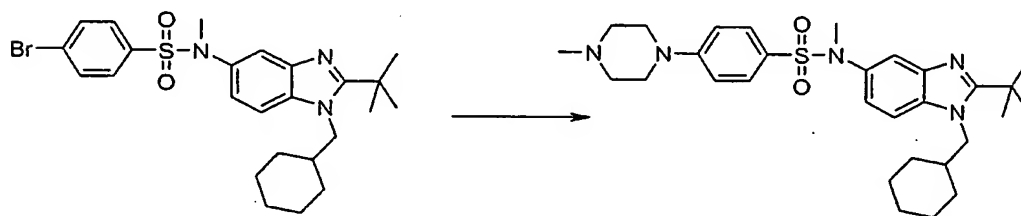


N-1-(Cyclohexylmethyl)-2-(1,1-dimethylethyl)-*N*-methyl-1*H*-benzimidazol-5-amine hydrogen chloride (532.2 mg, 1.39 mmol), DMAP (679.3 mg, 5.56 mmol) and 4-bromobenzene sulfonyl chloride (426.7 mg, 1.67 mmol) in MeCN (50 mL) were stirred overnight at rt. The reaction mixture was quenched with saturated NaHCO₃ (10 mL), evaporated to small volume and extracted with EtOAc (3x50 mL). The

combined organic phases were washed with brine and dried over Na₂SO₄. After evaporation of the solvent, the product was purified by MPLC using Hexanes/EtOAc (1:1) on silica to give 529.6 mg (74%) of a white solid as the title product. A small amount of the title product was converted to the corresponding TFA salt. ¹H NMR (400 MHz, METHANOL-D₄) δ 1.26 (m, 5 H), 1.64 (m, 2 H), 1.67 (s, 9 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 3.29 (s, 3 H), 4.45 (d, J=7.62 Hz, 2 H), 7.31 (m, 1 H), 7.45 (m, 2 H), 7.53 (d, J=1.56 Hz, 1 H), 7.72 (m, 2 H), 7.85 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 518.2.

10 Example 40

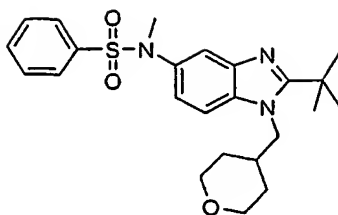
N-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(4-methyl-1-piperazinyl)-benzenesulfonamide



- 15 4-Bromo-*N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzenesulfonamide (50.1 mg, 0.093 mmol) and 1-methylpiperazine (0.2 mL, 180 mg, 1.79 mmol) in DMF (2 mL) were placed in a sealed tube. The mixture was heated at 220°C in a Personal Chemistry SmithSynthesizer microwave instrument for 4 h. After evaporation, the residue was purified by reversed-phase HPLC using 15-
20 60% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 43.73 mg (72%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.25 (m, 5 H), 1.64 (m, 2 H), 1.67 (s, 9 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 2.97 (s, 3 H), 3.18 (m, 4 H), 3.24 (s, 3 H), 3.60 (m, 2 H), 4.08 (m, 2 H), 4.45 (d, J=7.62 Hz, 2 H), 7.09 (m, 2 H), 7.31 (m, 1 H), 7.46 (m, 2 H), 7.59
25 (d, J=1.95 Hz, 1 H), 7.83 (m, 1 H); MS (ESI) (M+H)⁺ 538.3.

Example 41

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



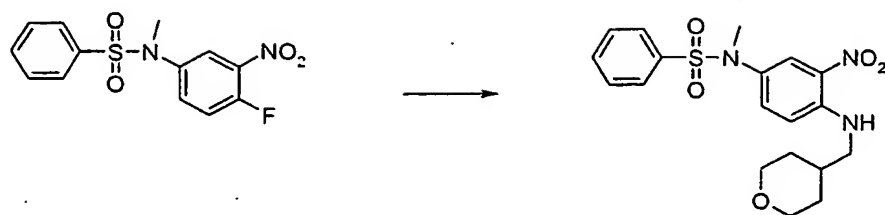
Step A. *N*-[2-*tert*-Butyl-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



5 Following the procedure for Step E in Example 4, using *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-yl)methyl]amino]phenyl}-*N*-methylbenzenesulfonamide (109 mg, 0.290 mmol) (for preparation, see the following steps B and C), trimethylacetyl chloride (0.039 mL, 0.319 mmol) and DMAP (7 mg, 0.058 mmol) in 3 mL of DCM. The
10 second step was performed in 2 mL of glacial acetic acid. The final product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 60 mg (37%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.55 (m, 2H), 1.60 (m, 2H), 1.68 (s, 9H), 2.37 (m, 1H), 3.27 (s, 3H), 3.36 (ddd, *J* = 11.57, 2.64 Hz, 2H), 3.93 (d, *J* = 3.52 Hz, 1H), 3.96
15 (m, 1H), 4.53 (d, *J* = 7.42 Hz, 2H), 7.31 (dd, *J* = 8.98, 1.95 Hz, 1H), 7.54 (m, 5H), 7.68 (m, 1H), 7.89 (d, *J* = 8.98 Hz, 1H); MS (ESI) (*M*+H)⁺ 442.3.

Step B. *N*-Methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-yl)methyl]amino}phenyl}benzenesulfonamide

20



Following the procedure for Step C in Example 1, using *N*-(4-fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide (100 mg, 0.322 mmol), 4-aminomethyltetrahydropyran (45 mg, 0.386 mmol) and TEA (0.070 mL, 0.483 mmol) in 3 mL of EtOH. The residue was dissolved in EtOAc and washed with 5% KHSO₄ solution, saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using a linear gradient of 30-50% EtOAc / hexanes. Yield: 123 mg (94%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.44 (m, 2H), 1.74 (m, 1H), 1.77 (m, 1H), 1.96 (m, 1H), 3.13 (s, 3H), 3.23 (dd, *J* = 6.74, 5.57 Hz, 2H), 3.43 (ddd, *J* = 11.81, 2.15, 2H), 4.40 (dd, *J* = 11.13, 3.91 Hz, 2H), 6.84 (d, *J* = 9.18 Hz, 1H), 7.49 (m, 3H), 7.61 (m, 3H), 8.21 (m, 1H).

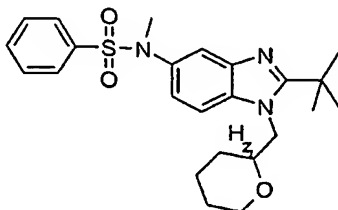
Step C. *N*-(3-Amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl)-*N*-methylbenzenesulfonamide



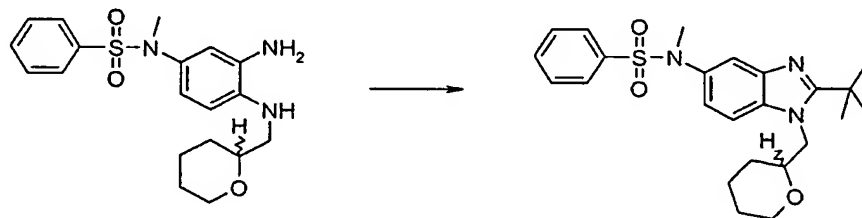
Following the procedure for Step E in Example 3, using *N*-methyl-*N*-(3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl)benzenesulfonamide (118 mg, 0.291 mmol) and a catalytic amount of 10% Pd/C in 20 mL of EtOAc. Yield: 109 mg (99%); MS (ESI) (*M*+*H*)⁺ 376.16.

Example 42

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide**

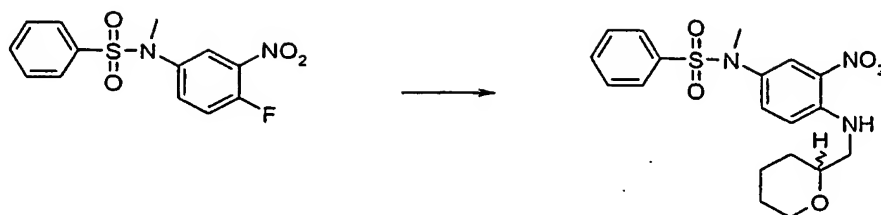


- 5 **Step A. *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide**



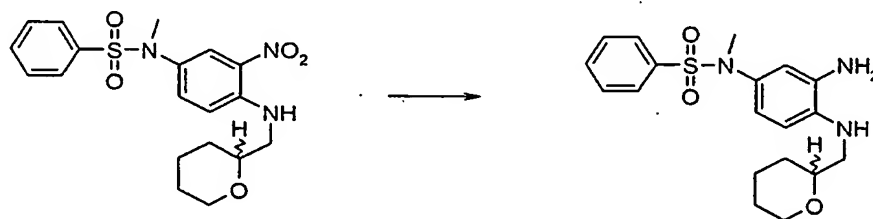
- Following the procedure for Step E in Example 4, using *N*-{3-Amino-4-[(tetrahydro-2*H*-pyran-2-ylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide (47 mg, 0.125 mmol) (for preparation, see the following steps B and C), trimethylacetyl chloride (0.017 mL, 0.138 mmol) and DMAP (3 mg, 0.025 mmol) in 3 mL of DCM. The second step was performed in 2 mL of glacial acetic acid. The final product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 33 mg (48%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.50 (m, 2H), 1.58 (m, 3H), 1.67 (s, 9H), 1.88 (m, 1H), 1.91 (m, 1H), 3.22 (ddd, *J* = 11.47, 2.64 Hz, 1H), 3.27 (s, 3H), 3.85 (m, 2H), 4.65 (m, 2H), 7.29 (dd, *J* = 9.08, 2.05 Hz, 1H), 7.51 (d, *J* = 1.56 Hz, 1H), 7.54 (m, 3H), 7.68 (m, 1H), 7.87 (d, *J* = 8.98 Hz, 1H); MS (ESI) (*M*+*H*)⁺ = 442.3. Anal. Calcd for C₂₄H₃₁N₃O₃S+1.5 TFA + 0.1 H₂O: C, 52.78; H, 5.36; N, 6.84. Found: C, 52.83; H, 5.37; N, 6.90.

Step B. *N*-Methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-2-ylmethyl)amino]phenyl}benzenesulfonamide



Following the procedure for Step C in Example 1, using *N*-(4-fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide (50 mg, 0.161 mmol), 2-aminomethyltetrahydropyran hydrochloride (30 mg, 0.193 mmol) and TEA (0.056 mL, 0.403 mmol) in 3 mL of EtOH. The residue was dissolved in EtOAc and washed with 5% KHSO₄ solution, saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using first DCM and then EtOAc as eluent. Yield: 58 mg (89%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.46 (m, 1H), 1.55 (d, J = 7.03Hz, 2H), 1.60 (m, 2H), 1.67 (m, 1H), 1.91 (m, 1H), 3.13 (s, 3H), 3.29 (m, 1H), 3.37 (m, 1H), 3.50 (ddd, J = 11.33, 2.93Hz, 1H), 3.62 (m, 1H), 4.06 (m, 1H), 6.83 (d, J = 9.37Hz, 1H), 7.46 (dd, J = 9.37, 2.54Hz, 1H), 7.50 (m, 2H), 7.57 (m, 2H), 7.61 (m, 1H), 8.33 (m, 1H).

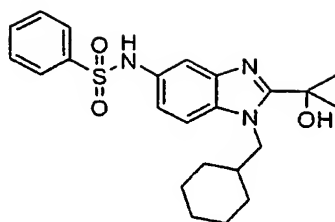
Step C. *N*-{3-Amino-4-[(tetrahydro-2*H*-pyran-2-ylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide



Following the procedure for Step E in Example 3, using *N*-methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-2-ylmethyl)amino]phenyl}benzenesulfonamide (55 mg, 0.136 mmol) and a catalytic amount of 10% Pd/C in 15 mL of EtOAc. Yield: 47 mg (92%); MS (ESI) (M+H)⁺ 376.17.

Example 43

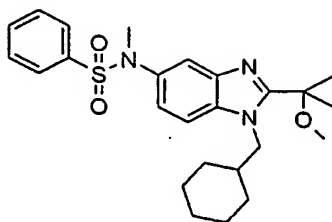
***N*-[1-(cyclohexylmethyl)-2-(1-hydroxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide**



Diisopropylethylamine (291.4 mg, 2.25 mmol) was added into a solution of *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzene sulfonamide (540.1 mg, 1.50 mmol) (for preparation, see Steps B and C in Example 7) and 2-hydroxy isobutyric acid (171.8 mg, 1.65 mmol) in DMF (15 mL) at 0 °C. Stirring for 20 min., HATU (684.4 mg, 1.80 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, diluted with water (100 mL), and extracted with EtOAc (2x50 mL). The combined organic phases were washed with NaCl (20 mL) and dried with anhydrous sodium sulphate. After filtration and concentration, the residue was dissolved in acetic acid (5 mL) in a sealed tube. The solutions were heated at 140°C using a Personal Chemistry Smith Synthesizer microwave instrument for 30 min. Upon evaporation of the solvent, the residue was diluted with EtOAc (100 mL), washed with 2N NaOH(10 mL), sat. NaCl (2x10 mL) and dried over anhydrous sodium sulphate. After filtration and evaporation, the residue was purified by MPLC (EtOAc on silica gel) to give 364.6 mg (57%) of a white solid as the title compound. Part of the product was converted to TFA salt. ¹H NMR (400 MHz, CD₃OD): δ 1.17 (m, 5 H), 1.56 (m, 2 H), 1.70 (m, 3 H), 1.76 (s, 6 H), 2.09 (m, 1 H), 4.48 (d, J=7.62 Hz, 2 H), 7.23 (m, 1 H), 7.47 (m, 2 H), 7.56 (m, 2 H), 7.72 (d, J=8.98 Hz, 1 H), 7.79 (m, 2 H); MS (ESI) (M+H)⁺ = 428.0; Anal. Calcd for C₂₃H₂₉N₃O₃S+1.2TFA: C, 54.05; H, 5.39; N, 7.45. Found: C, 54.09; H, 5.50; N, 7.42.

Example 44

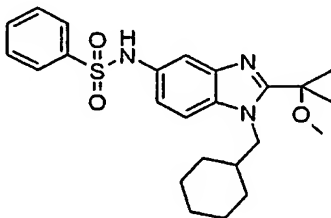
N-[1-(cyclohexylmethyl)-2-(1-methoxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzenesulfonamide



Sodium hydride (31.2 mg, 0.78 mmol) was added into a solution of *N*-[1-(cyclohexylmethyl)-2-(1-hydroxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide (111.0 mg, 0.26 mmol) (for preparation, see Example 43) in THF (10 mL) at 0 °C. Stirring for 30 min., methyl iodide (145.9 mg, 1.03 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, quenched with saturated NaHCO₃ (2 mL), and extracted with EtOAc (2x50 mL). The combined organic phases were washed with NaCl (20 mL) and dried with anhydrous sodium sulphate. After filtration and concentration, the residue was purified by MPLC (Hex/EtOAc (1:1) on silica gel) to give 110.3mg (93%) of colorless syrup as the title compound, which was converted to TFA salt as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 1.21 (m, 5 H), 1.62 (m, 2 H), 1.70 (m, 1 H), 1.76 (m, 2 H), 1.79 (s, 6 H), 2.13 (m, 1 H), 3.27 (s, 3 H), 3.31 (s, 3 H), 4.46 (d, J=7.62 Hz, 2 H), 7.24 (m, 1 H), 7.47 (m, 1 H), 7.55 (m, 4 H), 7.67 (m, 1 H), 7.76 (m, 1 H); MS (ESI) (M+H)⁺ = 456.0; Anal. Calcd for C₂₅H₃₃N₃O₃S+0.8TFA+0.6H₂O: C, 57.29; H, 6.33; N, 7.54. Found: C, 57.34; H, 6.31; N, 7.33.

Example 45

N-[1-(cyclohexylmethyl)-2-(1-methoxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide

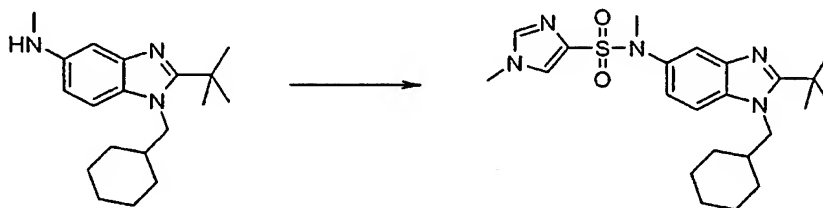


Following the same procedure in Example 44, using sodium hydride (25.0 mg, 0.63 mmol), *N*-[1-(cyclohexylmethyl)-2-(1-hydroxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide (89.3 mg, 0.21 mmol) (for preparation, see Example 43) and

methyl iodide (27.4 mg, 0.19 mmol) in THF (10 mL). The desired title compound was purified by MPLC (Hex/EtOAc (1:1) on silica gel) to give 34.8 mg (38%) of colorless syrup, which was converted to TFA salt as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 1.18 (m, 5 H), 1.59 (m, 2 H), 1.68 (m, 1 H), 1.74 (m, 2 H), 1.78 (s, 6 H), 2.09 (m, 1 H), 3.30 (s, 3 H), 4.42 (d, J=7.42 Hz, 2 H), 7.23 (dd, J=9.08, 2.05 Hz, 1 H), 7.47 (m, 2 H), 7.55 (m, 1 H), 7.58 (d, J=2.15 Hz, 1 H), 7.72 (d, J=9.18 Hz, 1 H), 7.80 (m, 2 H); MS (ESI) (M+H)⁺ = 442.0; Anal. Calcd for C₂₄H₃₁N₃O₃S+0.9TFA+0.5H₂O: C, 56.01; H, 5.99; N, 7.60. Found: C, 55.97; H, 6.00; N, 7.47.

Example 46

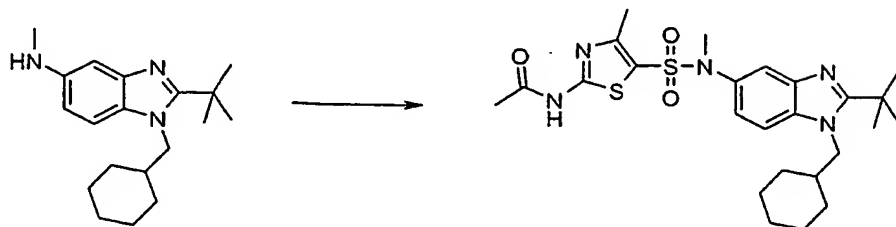
N-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,1-dimethyl-1*H*-imidazole-4-sulfonamide



- Following the same procedure of Step A in Example 4 using 2-*tert*-butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (40 mg, 0.134 mmol), 1-methyl-1*H*-imidazole-4-sulphonyl chloride (31 mg, 0.174 mmol) in 3 mL of DCM containing a catalytic amount of DMAP. The solvent was evaporated and the product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 62 mg (82%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.22 (m, 5 H), 1.62 (s, 2 H), 1.64 (s, 9 H), 1.67 (s, 1 H), 1.75 (m, 2 H), 2.08 (m, 1 H), 3.30 (s, 3 H), 3.73 (s, 3 H), 4.43 (d, J=7.62 Hz, 2 H), 7.44 (dd, J=8.98, 2.15 Hz, 1 H), 7.60 (d, J=1.37 Hz, 1 H), 7.65 (d, J=1.56 Hz, 1 H), 7.74 (d, J=0.98 Hz, 1 H), 7.82 (d, J=8.59 Hz, 1 H); MS (ESI) (M+H)⁺ 444.0; Anal. Calcd for C₂₃H₃₃N₅O₂S + 2.0 TFA + 0.1 H₂O: C, 48.15; H, 5.27; N, 10.40. Found: C, 48.06; H, 5.21; N, 10.55.

Example 47

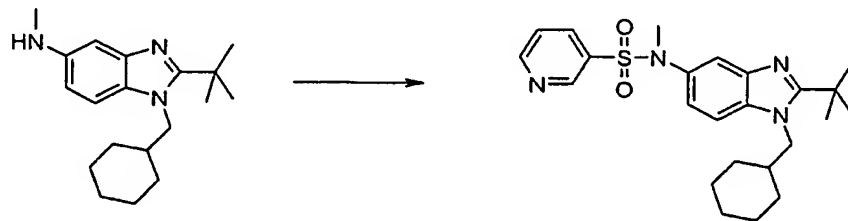
N-(5-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-4-methyl-1,3-thiazol-2-yl)acetamide



- 5 Following the same procedure of Step A in Example 4 using 2-*tert*-butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (40 mg, 0.134 mmol), 2-acetamido-4-methyl-5-thiazolesulfonyl chloride (44 mg, 0.174 mmol) in 3 mL of DCM containing a catalytic amount of DMAP. The solvent was evaporated and the product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and
- 10 lyophilized affording the title compound as the corresponding TFA salt. Yield: 51 mg (60%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.21 (m, 6 H), 1.59 (m, 2 H), 1.65 (m, 11 H), 2.08 (m, 4 H), 2.16 (s, 3 H), 3.32 (s, 3 H), 4.44 (d, J=7.81 Hz, 2 H), 7.41 (dd, J=9.08, 2.05 Hz, 1 H), 7.66 (d, J=1.76 Hz, 1 H), 7.86 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 518.0; Anal. Calcd for C₂₅H₃₅N₅O₃S₂ + 1.6 TFA + 0.4 H₂O: C, 47.88;
- 15 H, 5.33; N, 9.90. Found: C, 47.88; H, 5.28; N, 10.02.

Example 48

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpyridine-3-sulfonamide



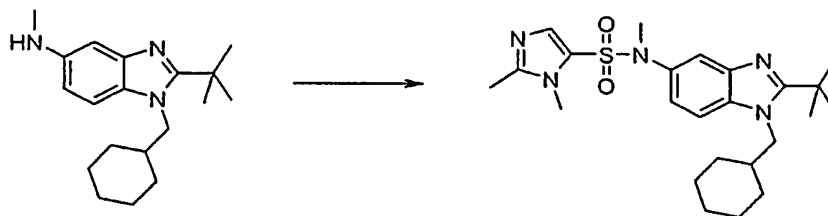
20

Following the same procedure of Step A in Example 4 using 2-*tert*-butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (65 mg, 0.217 mmol), 3-pyridinesulfonyl chloride hydrochloride (70 mg, 0.325 mmol) in 3 mL of DCM

containing a catalytic amount of DMAP. The solvent was evaporated and the product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 81 mg (67%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.23 (m, 5 H), 1.62 (m, 2 H), 1.66 (s, 9 H), 1.69 (m, 1 H), 1.76 (m, 2 H), 2.09 (m, 1 H), 3.31 (s, 3 H), 4.45 (d, J=7.62 Hz, 2 H), 7.32 (dd, J=8.98, 2.15 Hz, 1 H), 7.58 (d, J=1.56 Hz, 1 H), 7.61 (dd, J=8.01, 4.88 Hz, 1 H), 7.87 (d, J=8.98 Hz, 1 H), 8.02 (dt, J=8.15, 1.88 Hz, 1 H), 8.59 (s, 1 H), 8.81 (s, 1 H); MS (ESI) (M+H)⁺ 441.0; Anal. Calcd for C₂₄H₃₂N₄O₂S + 2.0 TFA + 0.5 H₂O: C, 49.63; H, 5.21; N, 8.27. Found: C, 49.69; H, 5.20; N, 8.29.

Example 49

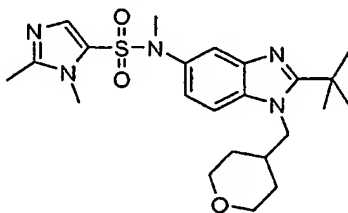
N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,1,2-trimethyl-1*H*-imidazole-5-sulfonamide



- Following the same procedure of Step A in Example 4 using 2-*tert*-butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (40 mg, 0.134 mmol), 1,2-dimethylimidazole-5-sulphonyl chloride (39 mg, 0.201 mmol) in 3 mL of DCM containing a catalytic amount of DMAP. The solvent was evaporated and the product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 65 mg (85%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.25 (m, 5 H), 1.64 (m, 2 H), 1.69 (s, 10 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 2.59 (s, 3 H), 3.40 (s, 3 H), 3.49 (s, 3 H), 4.48 (d, J=7.62 Hz, 2 H), 7.53 (dd, J=8.98, 1.95 Hz, 1 H), 7.78 (d, J=1.95 Hz, 1 H), 7.92 (s, 1 H), 7.95 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 458.3; Anal. Calcd for C₂₄H₃₅N₅O₂S + 3.0 TFA + 0.9 H₂O: C, 44.16; H, 4.92; N, 8.58. Found: C, 44.24; H, 5.00; N, 8.43.

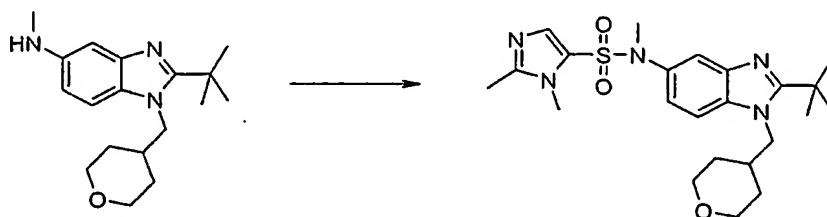
Example 50

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,1,2-trimethyl-1*H*-imidazole-5-sulfonamide**



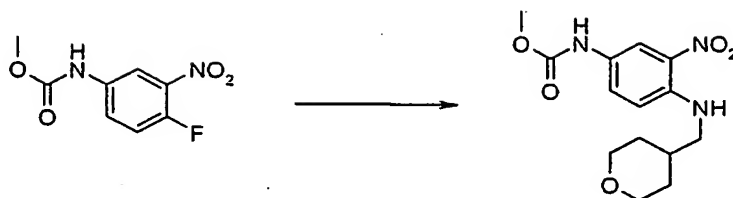
5

Step A: *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,1,2-trimethyl-1*H*-imidazole-5-sulfonamide



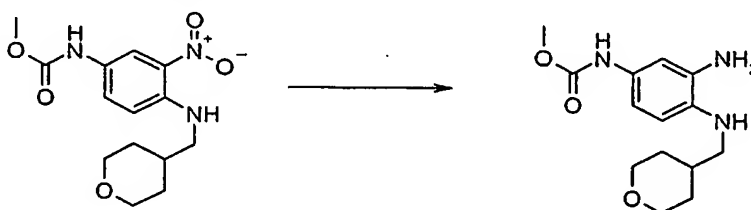
- 2-*tert*-Butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine
 (see following Steps B, C, D and E for preparation) (42 mg, 0.139 mmol) and 1,2-
 dimethylimidazole-5-sulphonyl chloride (33 mg, 0.167 mmol) were stirred in 3 mL of
 DCM containing a catalytic amount of DMAP overnight at rt. The solvent was
 evaporated and the product was purified by reversed-phase HPLC using 10-70%
 CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA
 salt. Yield: 64 mg (80%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.50 - 1.56 (m,
 2 H), 1.57 - 1.64 (m, 2 H), 1.68 (s, 9 H), 2.32 - 2.41 (m, 1 H), 2.58 (s, 3 H), 3.33 (dt,
 J= 11.42, 2.34 Hz, 2 H), 3.38 (s, 3 H), 3.49 (s, 3 H), 3.90 - 3.93 (m, 1 H), 3.95 (d,
 J=2.54 Hz, 1 H), 4.54 (d, J=7.62 Hz, 2 H), 7.52 (dd, J=8.98, 2.15 Hz, 1 H), 7.76 (d,
 J=1.56 Hz, 1 H), 7.89 (s, 1 H), 7.96 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 460.0;
 Anal. Calcd for C₂₃H₃₃N₅O₃S + 2.1 TFA + 2.3 H₂O: C, 44.12; H, 5.40; N, 9.72.
 Found: C, 43.89; H, 5.02; N, 10.12.

Step B: Methyl {3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}carbamate



Methyl (4-fluoro-3-nitrophenyl)carbamate (2.0g, 9.32 mmol) and 4-aminomethyl tetrahydropyran (1.28g, 11.2 mmol) were stirred in 50 mL of EtOH containing TEA (2.0 mL, 14.0 mmol) at 75°C for 48h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous 5% KHSO₄, saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes : EtOAc as eluent. Yield: 2.53g (88%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.42 (ddd, *J*=25.24, 12.06, 4.49 Hz, 2 H), 1.73 (d, *J*=1.76 Hz, 1 H), 1.76 (d, *J*=1.95 Hz, 1 H), 1.88 - 2.01 (m, 1 H), 3.22 (dd, *J*=6.74, 5.57 Hz, 2 H), 3.42 (td, *J*=11.86, 2.05 Hz, 2 H), 3.78 (s, 3 H), 4.01 (d, *J*=4.30 Hz, 1 H), 4.04 (d, *J*=3.51 Hz, 1 H), 6.48 (br.s, 1 H), 6.85 (d, *J*=9.37 Hz, 1 H), 7.65 (br.s, 1 H), 8.03 - 8.09 (m, 2 H).

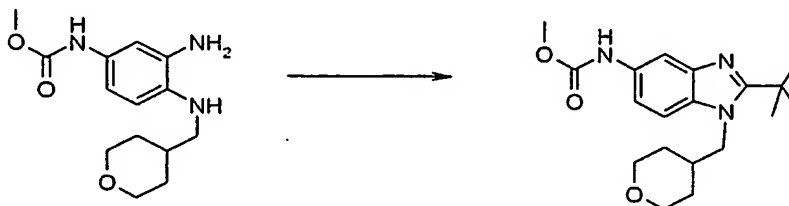
Step C: Methyl {3-amino-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}carbamate



Methyl {3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}carbamate (2.53 g, 8.18 mmol) was dissolved in 50 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken under H₂ atmosphere (40 psi) using a Parr hydrogenation apparatus overnight at rt. The solution was filtered through celite and the solvent was evaporated. Yield: 2.29 g (99%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.40 (ddd, *J*=25.09, 12.01, 4.49 Hz, 2 H), 1.70 - 1.74 (m, 1 H), 1.74 - 1.77 (m, 1 H), 1.81 - 1.92 (m, 1 H), 2.99 (d, *J*=6.64 Hz, 2 H), 3.34 (br.s, 2 H), 3.41 (dt, *J*=11.81, 2.15 Hz, 2 H), 3.74 (s, 3 H), 3.99 (d, *J*=3.51 Hz, 1 H), 4.02 (d,

$J=3.51$ Hz, 1 H), 6.38 (br.s, 1 H), 6.55 - 6.60 (m, 1 H), 6.62 - 6.68 (m, 1 H), 6.95 (br.s, 1 H).

Step D: Methyl [2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]carbamate



Methyl {3-amino-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl} carbamate (2.29 g, 8.20 mmol) and DMAP (0.20 g, 1.64 mmol) were dissolved in 75 mL of DCM. Trimethylacetyl chloride (1.10 mL, 9.02 mmol) was added dropwise and the solution was stirred at rt for 2h. The solution was washed with aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The residue was dissolved in 25 mL of AcOH and was heated at 125°C for 1h using a Personal Chemistry microwaves apparatus. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using 4:3 / hexanes : acetone as eluent. Yield: 1.81 g (64%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.48 - 1.54 (m, 4 H) 1.56 (s, 9 H) 2.23 - 2.35 (m, 1 H) 3.27 - 3.35 (m, 2 H) 3.78 (s, 3 H) 3.96 (t, $J=2.93$ Hz, 1 H) 3.99 (t, $J=3.03$ Hz, 1 H) 4.18 (d, $J=7.42$ Hz, 2 H) 6.63 (br.s, 1 H) 7.24 - 7.28 (m, 1 H) 7.41 (br.s, 1 H) 7.61 (d, $J=1.95$ Hz, 1 H).

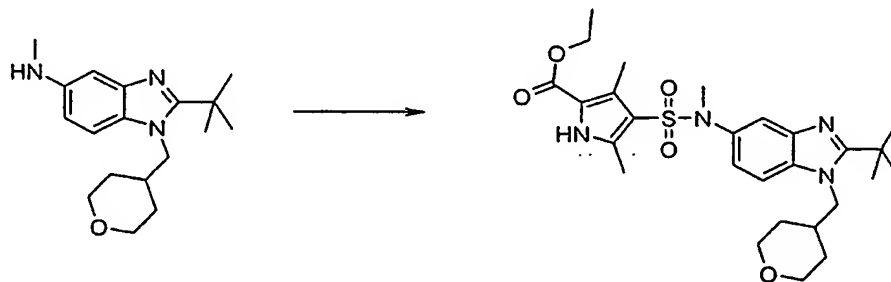
Step E: 2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine



Methyl [2-*tert*-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]carbamate (1.80 g, 5.21 mmol) was dissolved in 75 mL of THF at 0°C. 1M HCl/ether (7.3 mL, 7.29 mmol) was added dropwise and the solution was stirred at 0°C for 15 min. LiAlH₄ (988 mg, 26.1 mmol) was added slowly and the solution was stirred at rt overnight. The reaction was quenched at 0°C by the addition of MeOH (5 mL) followed by water (10 mL) and the solution was left to stir at rt for 30 min. Anhydrous Na₂SO₄ (10 g) was added and the solution was stirred at rt for another 30 min. The solution was filtered and the solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. Yield: 1.54 g (98%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.49 - 1.53 (m, 4 H), 1.53 - 1.57 (m, 9 H), 2.22 - 2.32 (m, 1 H), 2.87 (s, 3 H), 3.26 - 3.35 (m, 2 H), 3.95 (t, *J*=3.03 Hz, 1 H), 3.97 - 4.00 (m, 1 H), 4.13 (d, *J*=7.42 Hz, 2 H), 6.61 (dd, *J*=8.59, 2.15 Hz, 1 H), 6.99 (d, *J*=1.95 Hz, 1 H), 7.11 (d, *J*=8.59 Hz, 1 H).

Example 51

Ethyl 4-[[[2-*tert*-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl]-3,5-dimethyl-1H-pyrrole-2-carboxylate

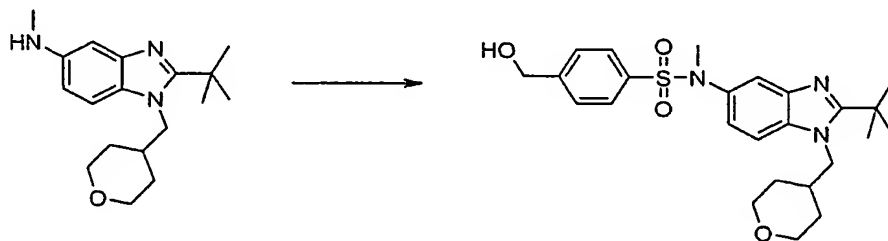


Following the same procedure as in Step A of Example 4 using 2-*tert*-butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (42 mg, 0.139 mmol), ethyl 4-(chlorosulfonyl)-3,5-dimethyl-1H-pyrrole-2-carboxylate (44 mg, 0.167 mmol) in 3 mL of DCM containing a catalytic amount of DMAP. The product was purified by reversed-phase HPLC using 10-70% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 61 mg (68%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.33 (t, *J*=7.13 Hz, 3 H), 1.45 - 1.53 (m, 2 H), 1.53 - 1.65 (m, 2 H), 1.68 (s, 9 H), 2.04 (s, 3 H), 2.16 (s, 3 H), 2.32 - 2.41 (m, 1 H), 3.24 (s, 3 H),

3.35 (td, $J=11.77$, 2.05 Hz, 2 H), 3.93 (d, $J=3.51$ Hz, 1 H), 3.96 (d, $J=3.51$ Hz, 1 H), 4.28 (q, $J=7.09$ Hz, 2 H), 4.54 (d, $J=7.62$ Hz, 2 H), 7.42 (dd, $J=9.08$, 2.05 Hz, 1 H), 7.65 (d, $J=1.56$ Hz, 1 H), 7.91 (d, $J=8.98$ Hz, 1 H); MS (ESI) ($M+H$)⁺ 531.2; Anal. Calcd for $C_{27}H_{38}N_4O_5S + 1.4$ TFA + 0.6 H_2O : C, 51.05; H, 5.84; N, 7.99. Found: C, 51.07; H, 5.91; N, 7.88.

Example 52

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(hydroxymethyl)-*N*-methylbenzenesulfonamide

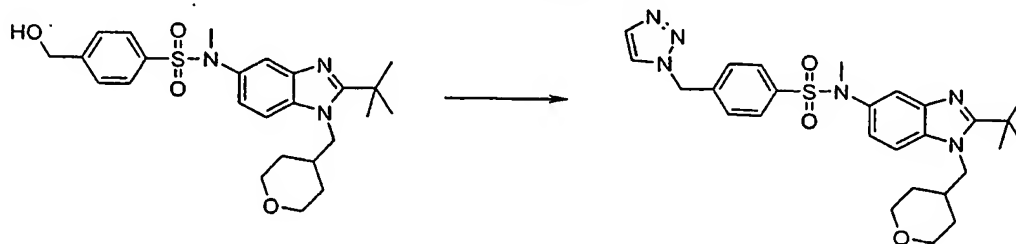


10

2-*tert*-Butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (35 mg, 0.116 mmol) and 4-formylbenzenesulfonyl chloride (29 mg, 0.139 mmol) were stirred in 3 mL of DCM containing a catalytic amount of DMAP at rt for 2h. The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. The residue was dissolved in MeOH (5 mL) and $NaCNBH_3$ (20 mg, 0.298 mmol) was added. The solution was stirred overnight at rt. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. The crude product was purified by silica gel flash chromatography using EtOAc as eluent. Yield: 55 mg (78%). 1H NMR (400 MHz, METHANOL- D_4) (TFA salt): δ 1.50 - 1.56 (m, 2 H), 1.57 - 1.65 (m, 2 H), 1.68 (s, 9 H), 2.31 - 2.41 (m, 1 H), 3.26 (s, 3 H), 3.35 (td, $J=11.57$, 2.64 Hz, 2 H), 3.93 (d, $J=3.32$ Hz, 1 H), 3.96 (d, $J=3.71$ Hz, 1 H), 4.52 (d, $J=7.42$ Hz, 2 H), 4.68 (s, 2 H), 7.30 (dd, $J=8.98$, 2.15 Hz, 1 H), 7.50 (s, 4 H), 7.54 (d, $J=1.56$ Hz, 1 H), 7.87 (d, $J=8.98$ Hz, 1 H); MS (ESI) ($M+H$)⁺ 472.0; Anal. Calcd for $C_{25}H_{33}N_3O_4S + 1.5$ TFA + 0.3 H_2O : C, 51.89; H, 5.46; N, 6.48. Found: C, 51.94; H, 5.48; N, 6.31.

Example 53

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(1*H*-1,2,3-triazol-1-ylmethyl)benzenesulfonamide

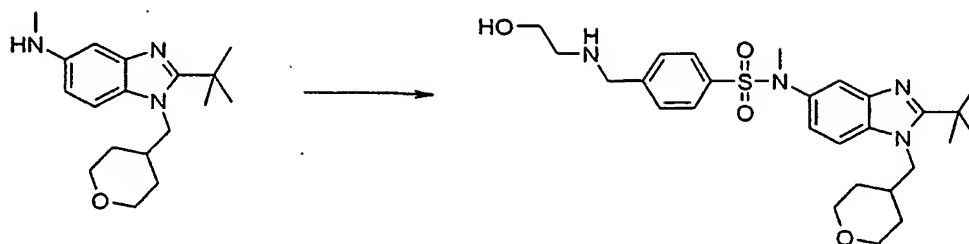


5

- N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(hydroxymethyl)-*N*-methylbenzenesulfonamide (55mg, 0.117 mmol) and TEA (0.025 mL, 0.176 mmol) were dissolved in 5 mL of DCM at 0°C. Methanesulfonyl chloride (0.011 mL, 0.140 mmol) was added dropwise and the solution was stirred at rt for 3h.
- 10 The solution was washed with aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. The residue was dissolved in 2 mL of DMF and KI (19 mg, 0.117 mmol) followed by 1*H*-1,2,3-triazole (0.135 mL, 2.34 mmol) were added. The solution was stirred at 80°C for 1h. The solvent was evaporated. The product was purified by reversed-phase HPLC using 10-70%
- 15 CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 35 mg (47%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.50 - 1.56 (m, 2 H), 1.56 - 1.65 (m, 2 H), 1.68 (s, 9 H), 2.32 - 2.40 (m, 1 H), 3.26 (s, 3 H), 3.35 (td, J=11.57, 2.64 Hz, 2 H), 3.93 (d, J=3.32 Hz, 1 H), 3.96 (d, J=3.51 Hz, 1 H), 4.52 (d, J=7.42 Hz, 2 H), 5.74 (s, 2 H), 7.31 (dd, J=8.98, 1.95 Hz, 1 H), 7.41 (d, J=8.59 Hz, 2 H), 7.54 (s, 1 H), 7.55 - 7.57 (m, 2 H), 7.79 (s, 1 H), 7.88 (d, J=8.98 Hz, 1 H), 8.09 (s, 1 H); MS (ESI) (M+H)⁺ 523.0; Anal. Calcd for C₂₇H₃₄N₆O₃S + 2.4 TFA: C, 47.96; H, 4.61; N, 10.55. Found: C, 48.02; H, 4.72; N, 10.22.
- 20

Example 54

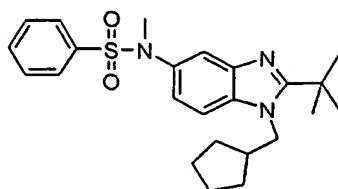
- 25 *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-[[[(2-hydroxyethyl)amino]methyl]-*N*-methylbenzenesulfonamide



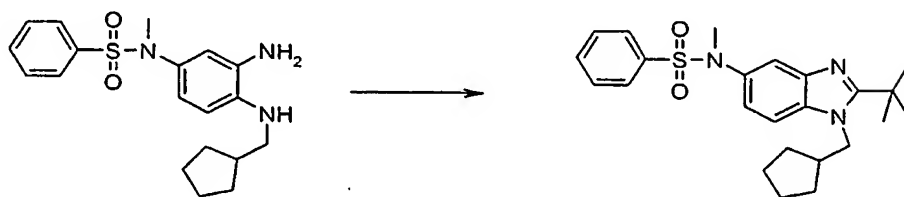
- 2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (58 mg, 0.192 mmol) and 4-formylbenzenesulfonyl chloride (47 mg, 0.230 mmol) were stirred in 5 mL of DCM containing a catalytic amount of DMAP at rt for 3h.
- 5 The solution was washed with aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. The residue was dissolved in MeOH (5 mL) containing a few drops of AcOH and 3Å molecular sieves. Ethanolamine (0.057 mL, 0.960 mmol) was added and the solution was stirred at rt for 30 min. NaCNBH₃ (36 mg, 0.576 mmol) was added and the solution was stirred
- 10 at rt for 3h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 48 mg (40%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.49 - 1.55 (m, 2 H), 1.55 - 1.61 (m, 2 H), 1.67 (s, 9 H), 2.32 - 2.39 (m, 1 H), 3.15 - 3.18 (m, 2 H), 3.27 (s, 3 H), 3.34 (dt, J=11.47, 2.64 Hz, 2 H), 3.81 (dd, J=5.96, 4.39 Hz, 2 H), 3.92 (d, J=3.12 Hz, 1 H), 3.95 (d, J=3.71 Hz, 1 H), 4.33 (s, 2 H), 4.51 (d, J=7.62 Hz, 2 H), 7.28 (dd, J=9.08, 2.05 Hz, 1 H), 7.56 (d, J=1.95 Hz, 1 H), 7.61 - 7.68 (m, 4 H), 7.85 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 515.2; Anal. Calcd for C₂₇H₃₈N₄O₄S + 2.7 TFA + 0.9 H₂O: C, 46.40; H, 5.11; N, 6.68. Found: C, 46.41; H, 5.05; N, 6.75.
- 20

Example 55

N-[2-tert-Butyl-1-(cyclopentylmethyl)-1H-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



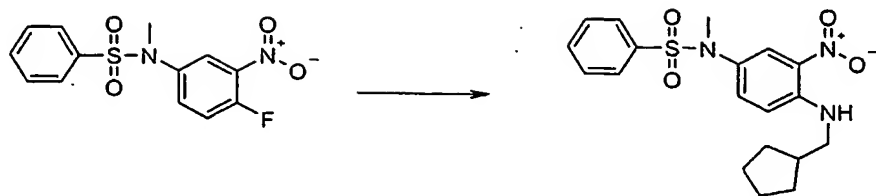
Step A: *N*-[2-*tert*-Butyl-1-(cyclopentylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



- 5 *N*-{3-Amino-4-[(cyclopentylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide (see following Steps B and C for preparation) (50 mg, 0.139 mmol) and trimethylacetyl chloride (0.019 mL, 0.153 mmol) were stirred in 2 mL of DCM containing a catalytic amount of DMAP at rt for 1h. The solvent was evaporated. The product was dissolved in 2 mL of AcOH and was stirred at 150°C for 40 min
- 10 using a Personal Chemistry microwaves instrument. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 26 mg (35%). ¹H NMR (400 MHz, METHANOL-
- 15 D₄): δ 1.47 (m, 2 H), 1.62 (m, 2 H), 1.68 (s, 9 H), 1.78 (m, 4 H), 2.51 (m, 1 H), 3.28 (s, 3 H), 4.61 (d, J=7.42 Hz, 2 H), 7.30 (dd, J=9.08, 2.05 Hz, 1 H), 7.54 (m, 5 H), 7.68 (m, 1 H), 7.87 (d, J=9.18 Hz, 1 H); MS (ESI) (M+H)⁺ 426.2; Anal. Calcd for C₂₄H₃₁N₃O₂S + 1.5 TFA + 0.9 H₂O: C, 52.92; H, 5.64; N, 6.96. Found: C, 52.80; H, 5.51; N, 7.35.

20

Step B: *N*-{4-[(Cyclopentylmethyl)amino]-3-nitrophenyl}-*N*-methylbenzenesulfonamide



N-(4-Fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide (for preparation see Example 3, Steps B and C) (50 mg, 0.161 mmol) and cyclopentylmethylamine (0.062 mL of a 1 g / 3 mL solution, 0.209 mmol) were stirred in 2 mL of EtOH containing TEA (0.025 mL, 0.241 mmol) at 75°C for 5h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with 5% aqueous KHSO₄ solution, aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using 3:1 / hexanes:EtOAc as eluent. Yield: 57 mg (91%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.31 (m, 3 H), 1.66 (m, 4 H), 1.91 (m, 2 H), 2.28 (m, 1 H), 3.13 (s, 3 H), 3.24 (dd, J=7.23, 5.08 Hz, 2 H), 6.84 (d, J=9.37 Hz, 1 H), 7.45 (dd, J=9.28, 2.64 Hz, 1 H), 7.50 (m, 2 H), 7.60 (m, 3 H), 8.17 (m, 1 H).

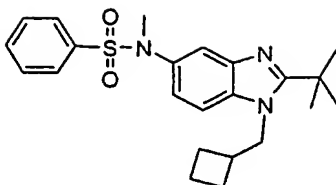
Step C: *N*-{3-Amino-4-[(cyclopentylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide



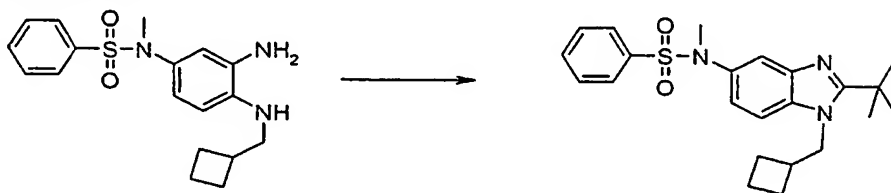
N-{4-[(Cyclopentylmethyl)amino]-3-nitrophenyl}-*N*-methylbenzenesulfonamide (55 mg, 0.141 mmol) was dissolved in 15 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken under H₂ atmosphere (40 psi) at rt for 3h. The solution was filtered through celite and the solvent was evaporated. Yield: 51 mg (99%). MS (ESI) (M+H)⁺ 360.26.

Example 56

***N*-[2-*tert*-Butyl-1-(cyclobutylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide**

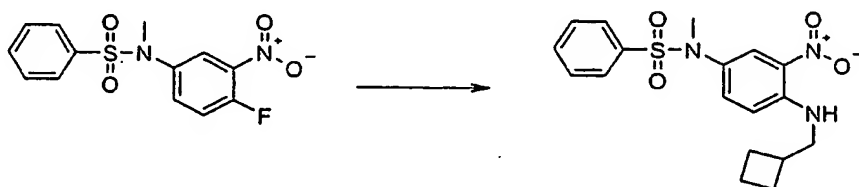


Step A: *N*-[2-*tert*-Butyl-1-(cyclobutylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



- 5 Following the same procedure used as in Step A in Example 3 using *N*-{3-amino-4-[(cyclobutylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide (for preparation see following Steps B and C) (53 mg, 0.153 mmol) and trimethylacetyl chloride (0.021 mL, 0.168 mmol) in 2 mL of DCM containing a catalytic amount of DMAP. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and
- 10 lyophilized affording the title compound as the corresponding TFA salt. Yield: 43 mg (53%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.66 (s, 9 H), 1.92 (m, 2 H), 2.10 (m, 4 H), 2.87 (m, 1 H), 3.27 (s, 3 H), 4.65 (d, J=6.44 Hz, 2 H), 7.30 (dd, J=8.98, 1.95 Hz, 1 H), 7.53 (m, 5 H), 7.68 (m, 1 H), 7.81 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 412.3; Anal. Calcd for C₂₃H₂₉N₃O₂S + 1.4 TFA + 0.8 H₂O: C, 52.92; H, 5.51; N, 7.18.
- 15 Found: C, 52.91; H, 5.46; N, 7.11.

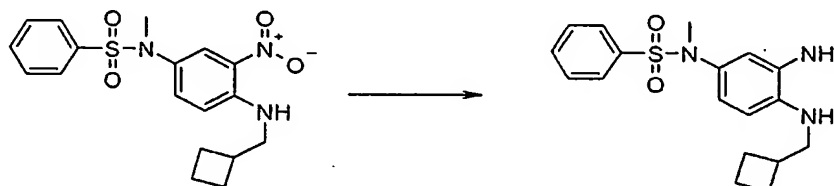
Step B: *N*-{4-[(Cyclobutylmethyl)amino]-3-nitrophenyl}-*N*-methylbenzenesulfonamide



- 20 Following the same procedure used as in Example 3, Step D using *N*-(4-fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide (for preparation see Example 3, Steps B and C) (50 mg, 0.161 mmol), cyclobutylmethylamine (0.040 mL of a 5.3M

solution/MeOH, 0.209 mmol) in 2 mL of EtOH containing TEA (0.025 mL, 0.242 mmol). The crude product was purified by silica gel flash chromatography using 3:1 / hexanes:EtOAc as eluent. Yield: 61 mg (99%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.56 (s, 2 H), 1.81 (m, 2 H), 1.95 (m, 1 H), 2.19 (m, 2 H), 3.13 (s, 3 H), 3.33 (dd, J=7.23, 5.08 Hz, 2 H), 6.83 (d, J=9.18 Hz, 1 H), 7.45 (dd, J=9.18, 2.54 Hz, 1 H), 7.51 (m, 2 H), 7.61 (m, 3 H), 8.04 (m, 1 H).

Step C: *N*-{3-Amino-4-[(cyclobutylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide



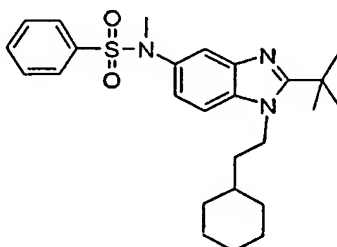
10

Following the same procedure used as in Example 3 Step E using *N*-{4-[(cyclobutylmethyl)amino]-3-nitrophenyl}-*N*-methylbenzenesulfonamide (58 mg, 0.154 mmol) in 15 mL of EtOAc containing a catalytic amount of 10% Pd/C. Yield: 53 mg (99%). MS (ESI) (M+H)⁺ 346.20.

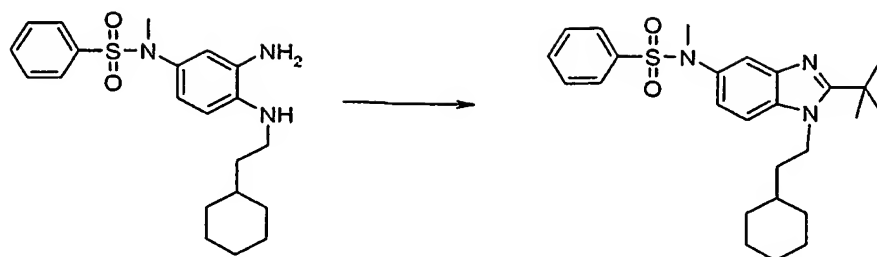
15

Example 57

***N*-[2-*tert*-Butyl-1-(2-cyclohexylethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide**

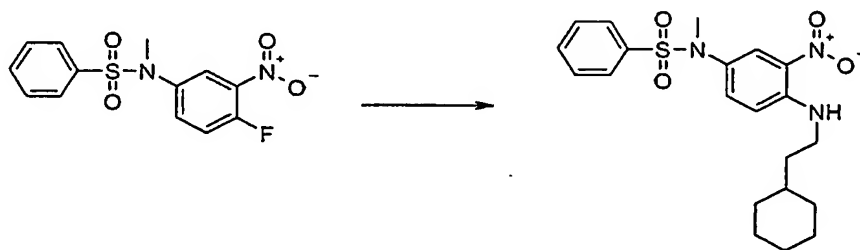


Step A: *N*-[2-*tert*-Butyl-1-(2-cyclohexylethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



Following the same procedure used as in Step A of Example 3 using *N*-{3-amino-4-[(2-cyclohexylethyl)amino]phenyl}-*N*-methylbenzenesulfonamide (for preparation see following Steps B and C) (56 mg, 0.145 mmol) and trimethylacetyl chloride (0.020 mL, 0.160 mmol) in 2 mL of DCM containing a catalytic amount of DMAP. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 37 mg (45%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.11 (ddd, J=23.92, 12.11, 2.83 Hz, 2 H), 1.34 (m, 3 H), 1.60 (m, 1 H), 1.66 (s, 9 H), 1.72 (m, 1 H), 1.77 (m, 1 H), 1.81 (m, 2 H), 1.85 (m, 2 H), 1.90 (m, 1 H), 3.27 (s, 3 H), 4.60 (m, 2 H), 7.33 (dd, J=8.98, 1.95 Hz, 1 H), 7.54 (m, 5 H), 7.68 (m, 1 H), 7.74 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 454.2; Anal. Calcd for C₂₆H₃₅N₃O₂S + 1.4 TFA: C, 56.40; H, 5.98; N, 6.85. Found: C, 56.48; H, 5.98; N, 6.99.

15 Step B: *N*-{4-[(2-Cyclohexylethyl)amino]-3-nitrophenyl}-*N*-methylbenzenesulfonamide

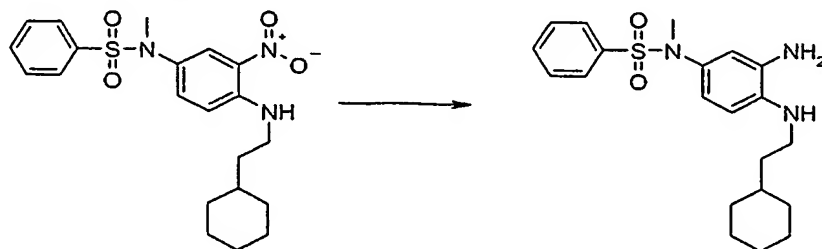


Following the same procedure used as in Example 3 Step D using *N*-(4-fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide (for preparation see Example 3, Steps B and C) (50 mg, 0.161 mmol), (2-cyclohexylethyl)amine hydrochloride (32 mg, 0.193 mmol) in 2 mL of EtOH containing TEA (0.060 mL, 0.402 mmol). The crude product was purified by silica gel flash chromatography using 4:1 / hexanes:EtOAc as

eluent. Yield: 65 mg (97%). ^1H NMR (400 MHz, CHLOROFORM-D): δ 0.99 (m, 2 H), 1.25 (m, 4 H), 1.43 (m, 1 H), 1.64 (m, 3 H), 1.72 (m, 1 H), 1.75 (m, 2 H), 1.78 (m, 1 H), 3.13 (s, 3 H), 3.33 (m, 2 H), 6.83 (d, $J=9.37$ Hz, 1 H), 7.46 (m, 1 H), 7.51 (m, 2 H), 7.58 (m, 2 H), 7.61 (m, 1 H), 8.08 (m, 1 H).

5

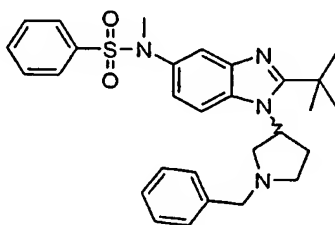
Step C: *N*-{3-Amino-4-[(2-cyclohexylethyl)amino]phenyl}-*N*-methylbenzenesulfonamide



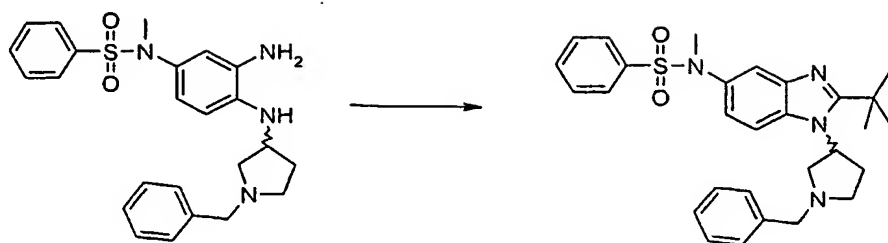
Following the same procedure used as in Example 3 Step E using *N*-{4-[(2-cyclohexylethyl)amino]-3-nitrophenyl}-*N*-methylbenzenesulfonamide (60 mg, 0.144 mmol) in 15 mL of EtOAc containing a catalytic amount of 10% Pd/C. Yield: 56 mg (99%). MS (ESI) ($M+H$) $^+$ 388.26.

Example 58

15 *N*-[1-(1-Benzylpyrrolidin-3-yl)-2-*tert*-butyl-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide

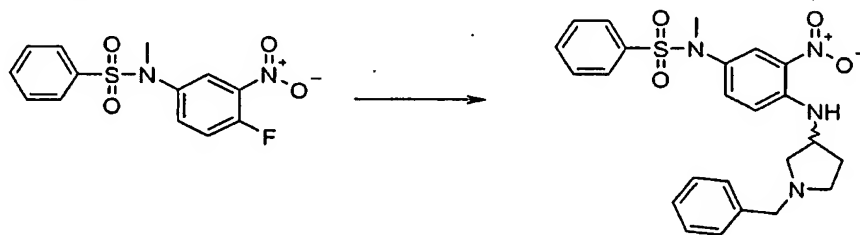


Step A: *N*-[1-(1-Benzylpyrrolidin-3-yl)-2-*tert*-butyl-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



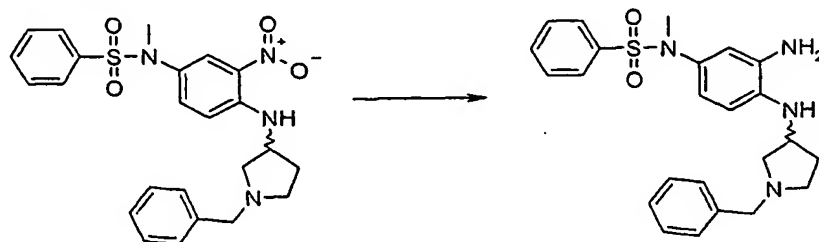
- Following the same procedure used as in Step A in Example 3 using *N*-{3-amino-4-[(1-benzylpyrrolidin-3-yl)amino]phenyl}-*N*-methylbenzenesulfonamide (for preparation see following Steps B and C) (75 mg, 0.172 mmol) and
- 5 trimethylacetyl chloride (0.025 mL, 0.189 mmol) in 5 mL of DCM containing a catalytic amount of DMAP. The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 48 mg (45%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.59 (s, 9 H), 2.61 (m, 1 H), 2.72 (m, 1 H), 3.23 (m, 3 H), 3.44 (m, 1 H), 3.66
- 10 (m, 1 H), 3.75 (m, 1 H), 3.81 (m, 1 H), 4.44 (m, 2 H), 5.85 (m, 1 H), 7.23 (dd, J=8.89, 2.05 Hz, 1 H), 7.43 (m, 4 H), 7.51 (m, 6 H), 7.65 (m, 1 H), 7.94 (d, J=7.81 Hz, 1 H); MS (ESI) (M+H)⁺ 503.2; Anal. Calcd for C₂₉H₃₄N₄O₂S + 2.3 TFA + 0.3 H₂O: C, 52.39; H, 4.83; N, 7.27. Found: C, 52.44; H, 4.87; N, 7.28.

- 15 **Step B: *N*-{4-[(1-Benzylpyrrolidin-3-yl)amino]-3-nitrophenyl}-*N*-methylbenzenesulfonamide**



- Following the same procedure used as in Example 3 Step D using *N*-(4-fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide (for preparation see Example 3, Steps B and C) (70 mg, 0.226 mmol), 1-benzylpyrrolidin-3-amine (50 mg, 0.271 mmol) in 3
- 20 mL of EtOH containing TEA (0.050 mL, 0.339 mmol). The crude product was purified by silica gel flash chromatography using 50 to 80% EtOAc in hexanes as eluent. Yield: 95 mg (90%). MS (ESI) (M+H)⁺ 466.99.

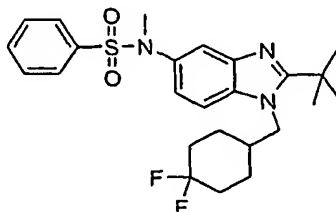
Step C: *N*-{3-Amino-4-[(1-benzylpyrrolidin-3-yl)amino]phenyl}-*N*-methylbenzenesulfonamide



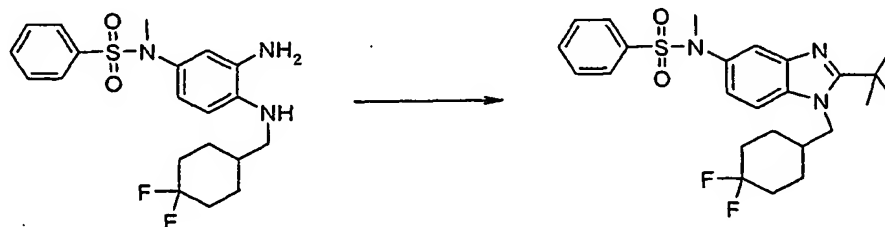
- 5 Following the same procedure used as in Example 3 Step E using *N*-{4-[(1-benzylpyrrolidin-3-yl)amino]-3-nitrophenyl}-*N*-methylbenzenesulfonamide (95 mg, 0.204 mmol) in 15 mL of EtOAc containing a catalytic amount of 10% Pd/C. Yield: 76 mg (85%). MS (ESI) (M+H)⁺ 437.02.

10 Example 59

***N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylbenzenesulfonamide**



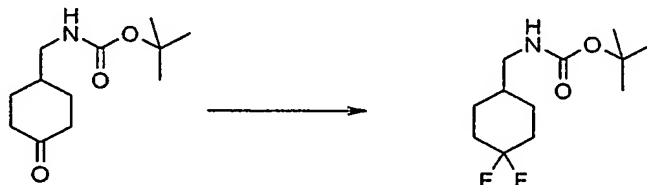
- 15 Step A: *N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylbenzenesulfonamide**



Following the same procedure used as in Step A of Example 3 using *N*-(3-amino-4-[(4,4-difluorocyclohexyl)methyl]amino)phenyl)-*N*-methylbenzenesulfonamide (for preparation see following Steps B, C, D and E) (61 mg, 0.149 mmol) and

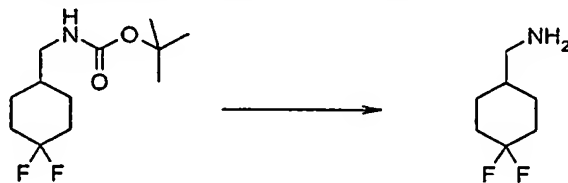
trimethylacetyl chloride (0.020 mL, 0.160 mmol) in 5 mL of DCM containing a catalytic amount of DMAP. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 25 mg (28%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.57 (s, 2 H), 1.67 (s, 9 H), 1.72 (s, 2 H), 1.76 (m, 1 H), 1.80 (m, 1 H), 2.07 (m, 2 H), 2.24 (m, 1 H), 3.27 (s, 3 H), 4.54 (d, J=7.62 Hz, 2 H), 7.31 (dd, J=8.98, 1.95 Hz, 1 H), 7.54 (m, 5 H), 7.68 (m, 1 H), 7.86 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 476.0; Anal. Calcd for C₂₅H₃₁N₃O₂SF₂ + 1.6 TFA: C, 51.47; H, 4.99; N, 6.39. Found: C, 51.46; H, 5.00; N, 6.53.

Step B: *tert*-Butyl [(4,4-difluorocyclohexyl)methyl]carbamate



4-N-Boc-aminomethyl cyclohexanone (1.00 g, 4.4 mmol) was dissolved in 30 mL of DCM at 0°C. DAST (1.45 mL, 11.0 mmol) was added dropwise and the solution was stirred at rt overnight. The solution was washed with aqueous 5% KHSO₄ solution, saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using 3:1 / hexanes : EtOAc as eluent. Yield: 508mg (46%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.19 - 1.36 (m, 2 H), 1.44 (s, 9 H), 1.51 - 1.56 (m, 1 H), 1.59 - 1.75 (m, 2 H), 1.75 - 1.84 (m, 2 H), 2.01 - 2.16 (m, 2 H), 3.03 (t, J=6.54 Hz, 2 H), 4.62 (br.s, 1 H).

Step C: [(4,4-Difluorocyclohexyl)methyl]amine hydrochloride



tert-Butyl [(4,4-difluorocyclohexyl)methyl]carbamate (505 mg, 2.03 mmol) was stirred in 5 mL of 1M HCl/AcOH at rt for 2h. The solvent was evaporated. The residue was washed with ether, filtered and dried. Yield: 330 mg (88%). ¹H NMR

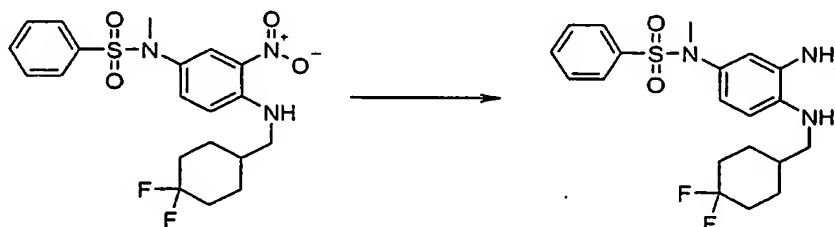
(400 MHz, METHANOL-D₄): δ 1.28 - 1.40 (m, 2 H), 1.71 - 1.82 (m, 2 H), 1.84 (d, $J=3.12$ Hz, 2 H), 1.86 - 1.89 (m, 1 H), 2.03 - 2.15 (m, 2 H), 2.85 (d, $J=7.03$ Hz, 2 H).

Step D: *N*-(4-[[[(4,4-Difluorocyclohexyl)methyl]amino]-3-nitrophenyl]-*N*-methylbenzenesulfonamide



Following the same procedure used as in Example 3 Step D using *N*-(4-fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide (for preparation see Example 3, Steps B and C) (50 mg, 0.161 mmol), [(4,4-difluorocyclohexyl)methyl]amine hydrochloride (35 mg, 0.193 mmol) in 3 mL of EtOH containing TEA (0.056 mL, 0.403 mmol). The crude product was purified by silica gel flash chromatography using 40% EtOAc in hexanes as eluent. Yield: 71 mg (99%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.42 (m, 2 H), 1.71 (m, 1 H), 1.80 (m, 2 H), 1.92 (m, 1 H), 1.96 (m, 1 H), 1.96 (m, 1 H), 2.17 (m, 2 H), 3.13 (s, 3 H), 3.24 (dd, $J=6.64, 5.66$ Hz, 2 H), 6.82 (d, $J=9.18$ Hz, 1 H), 7.48 (m, 2 H), 7.51 (m, 2 H), 7.61 (m, 3 H), 8.20 (t, $J=5.27$ Hz, 1 H).

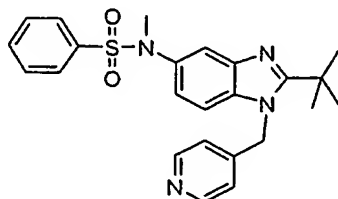
Step E: *N*-(3-Amino-4-[[[(4,4-difluorocyclohexyl)methyl]amino]phenyl]-*N*-methylbenzenesulfonamide



Following the same procedure used as in Example 3 Step E using *N*-(4-[[[(4,4-difluorocyclohexyl)methyl]amino]-3-nitrophenyl]-*N*-methylbenzenesulfonamide (65 mg, 0.148 mmol) in 20 mL of EtOAc containing a catalytic amount of 10% Pd/C. Yield: 61 mg (99%). MS (ESI) ($M+H$)⁺ 410.24.

Example 60

***N*-[2-*tert*-Butyl-1-(pyridin-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide**

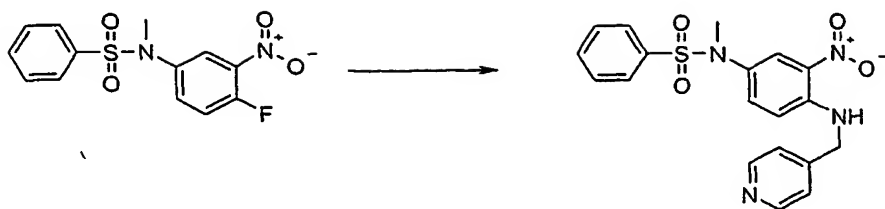


5 Step A: *N*-[2-*tert*-Butyl-1-(pyridin-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



Following the same procedure used as in Step A of Example 3 using *N*-{3-amino-4-[(pyridin-4-ylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide (for preparation see following Steps B and C) (63 mg, 0.171 mmol) and trimethylacetyl chloride (0.025 mL, 0.188 mmol) in 5 mL of DCM containing a catalytic amount of DMAP. The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 48 mg (51%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.57 (s, 9 H), 3.22 (s, 3 H), 6.08 (s, 2 H), 7.13 (dd, J=8.88, 2.05 Hz, 1 H), 7.29 (d, J=8.40 Hz, 1 H), 7.38 (d, J=4.88 Hz, 2 H), 7.49 (m, 4 H), 7.53 (m, 1 H), 7.63 (m, 1 H), 8.62 (m, 2 H); MS (ESI) (M+H)⁺ 435.0; Anal. Calcd for C₂₄H₂₆N₄O₂S + 2.3 TFA + 0.1 H₂O: C, 49.17; H, 4.11; N, 8.02. Found: C, 49.15; H, 4.10; N, 8.08.

20 Step B: *N*-Methyl-*N*-{3-nitro-4-[(pyridin-4-ylmethyl)amino]phenyl}benzenesulfonamide



N-(4-Fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide (for preparation see Example 3, Steps B and C) (105 mg, 0.338 mmol) and 4-(aminomethyl)pyridine (0.070 mL, 0.676 mmol) were stirred in 3 mL of CH₃CN at rt for 24h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using EtOAc as eluent. Yield: 102 mg (76%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 3.13 (s, 3 H), 4.61 (d, *J*=5.08 Hz, 2 H), 6.65 (dd, *J*=9.08, 1.07 Hz, 1 H), 7.25 - 7.29 (m, 2 H), 7.37 (dd, *J*=9.18, 2.73 Hz, 1 H), 7.47 - 7.53 (m, 2 H), 7.56 - 7.59 (m, 2 H), 7.60 - 7.65 (m, 1 H), 7.70 (d, *J*=2.54 Hz, 1 H), 8.50 - 8.54 (m, 1 H), 8.62 (d, *J*=5.47 Hz, 2 H).

Step C: *N*-{3-Amino-4-[(pyridin-4-ylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide



Following the same procedure used as in Example 3 Step E using *N*-methyl-*N*-{3-nitro-4-[(pyridin-4-ylmethyl)amino]phenyl}benzenesulfonamide (96 mg, 0.241 mmol) in 15 mL of EtOAc containing a catalytic amount of 10% Pd/C. Yield: 63 mg (71%). MS (ESI) (M+H)⁺ 368.94.

Example 61

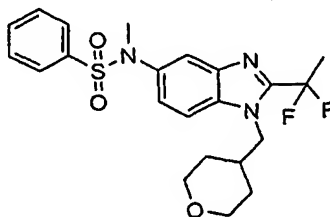
N-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



A solution of *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide (61.2 mg, 0.163 mmol) (for preparation, see the following steps B and C in Example 41) in trifluoroacetic acid (3 mL) was heated for 20 h at reflux. Upon evaporation, the residue was purified by reversed-phase HPLC using 20-70% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 38.3 mg (52%). ¹HNMR (400 MHz, CD₃OD): δ 1.40 - 1.50 (m, 4 H), 2.16 - 2.33 (m, 1 H), 3.25 (s, 3 H), 3.31 - 3.41 (m, 2 H), 3.86 - 4.00 (m, 2 H), 4.32 (d, *J*=7.62 Hz, 2 H), 7.32 (dd, *J*=8.88, 2.05 Hz, 1 H), 7.38 (d, *J*=1.76 Hz, 1 H), 7.48 - 7.58 (m, 4 H), 7.62 - 7.69 (m, 1 H), 7.72 (d, *J*=8.79 Hz, 1 H). MS (ESI) (*M*+*H*)⁺ = 454.0. Anal. Calcd for C₂₁H₂₂F₃N₃O₃S+ 0.20 TFA (476.29): C, 53.97; H, 4.70; N, 8.82; Found: C, 54.01; H, 4.73; N, 9.00.

Example 62

N-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide

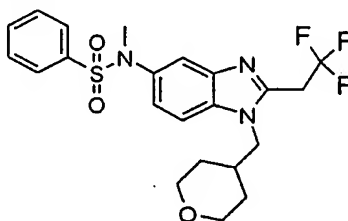


Diisopropylethylamine (56.9 mg, 0.44 mmol) was added into a solution of *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide (75.3 mg, 0.20 mmol) (for preparation, see the steps B and C in Example 41) and 2,2-difluoropropionic acid (23.1 mg, 0.21 mmol) in DMF (5 mL) at 0 °C. Stirring for 20 min, HATU (91.3 mg, 0.24 mmol) was added. The reaction mixture was stirred overnight at room temperature. After evaporation of the solvent, the residue was dissolved in acetic acid (10 mL) and heated for 12 h at 90 °C.

Upon evaporation of the solvent, the residue was diluted with EtOAc (100 mL), washed with 2 *N* NaOH (10 mL), saturated NaCl (2x10 mL) and dried over anhydrous sodium sulphate. After filtration and concentration, the crude product was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 71.4 mg (79%) of a white solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 1.28 - 1.45 (m, 4 H), 2.08 - 2.15 (m, 1 H), 2.21 (t, J=19.53 Hz, 3 H), 3.13 - 3.19 (m, 2 H), 3.19 (s, 3 H), 3.80 (m, 2 H), 4.28 (d, J=7.42 Hz, 2 H), 7.13 (dd, J=8.79, 1.95 Hz, 1 H), 7.36 (d, J=1.95 Hz, 1 H), 7.47 - 7.52 (m, 2 H), 7.53 - 7.63 (m, 2 H), 7.67 - 7.73 (m, 1 H), 7.75 (d, J=8.79 Hz, 1 H). MS (ESI) (M+H)⁺ = 450.0. Anal. Calcd for C₂₂H₂₅F₂N₃O₃S (449.52): C, 58.78; H, 5.61; N, 9.35; Found: C, 58.94; H, 5.51; N, 8.94.

Example 63

N-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(2,2,2-trifluoroethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



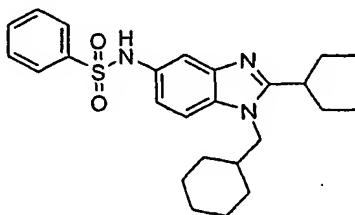
15

Following the procedure for Example 42, using *N*-{3-Amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide (150.6 mg, 0.40 mmol) (for preparation, see the steps B and C in Example 41), diisopropylethylamine (113.8 mg, 0.88 mmol) and 3,3,3-trifluoropropionic acid (56.3 mg, 0.44 mmol) and HATU (182.6 mg, 0.48 mmol) in DMF (10 mL) and then in acetic acid (5 mL), the crude product was purified by MPLC using EtOAc on silica gel to give 46.4 mg (32%) of a light yellow solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 1.39 - 1.56 (m, 4 H), 2.12 - 2.30 (m, 1 H), 3.25 (s, 3 H), 3.32 - 3.38 (m, 2 H), 3.88 - 3.96 (m, 2 H), 4.22 (q, J=9.96 Hz, 2 H), 4.31 (d, J=7.62 Hz, 2 H), 7.22 (dd, J=8.89, 2.05 Hz, 1 H), 7.39 (d, J=1.56 Hz, 1 H), 7.49 - 7.59 (m, 4 H), 7.63 - 7.68 (m, 1 H), 7.70 (d, J=8.98 Hz, 1 H). MS (ESI) (M+H)⁺ = 468.0. Anal. Calcd for C₂₂H₂₄F₃N₃O₃S + 1.10 TFA + 0.20 H₂O + 0.20 CH₃OH (602.95): C, 48.61; H, 4.40; N, 6.97; Found: C, 48.59; H, 4.31; N, 6.85.

25

Example 64

***N*-[1-(cyclohexylmethyl)-2-(1-ethylpropyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide**



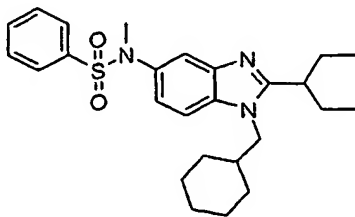
5

Following the procedure for Step A in Example 7, using *N*-(3-amino-4-[(cyclohexylmethyl)amino]phenyl)benzene sulfonamide (184.0mg, 0.51 mmol), DMAP (15.0 mg, 0.12 mmol) and 2-ethylbutyryl chloride (74.0 mg, 0.55 mmol) in CH₂Cl₂ (15 mL) and then in acetic acid (15 mL), the crude product was purified by
 10 MPLC using Hex/EtOAc (1:1) on silica gel. Yield: 164.4 mg (73%). ¹HNMR (400 MHz, CD₃OD): δ 0.92 (t, J=7.42 Hz, 6 H), 1.18 (m, 5 H), 1.57 (m, 2 H), 1.73 (m, 3 H), 1.83 (m, 2 H), 1.94 (m, 3 H), 3.33 (m, 1 H), 4.26 (d, J=7.62 Hz, 2 H), 7.25 (m, 1 H), 7.48 (m, 2 H), 7.57 (m, 2 H), 7.73 (d, J=8.98 Hz, 1 H), 7.81 (m, 2 H). MS (ESI) (M+H)⁺ = 440.0. Anal. Calcd for C₂₅H₃₃N₃O₂S+1.10 TFA+0.10 H₂O (566.85): C, 57.63; H, 6.10; N, 7.41; Found: C, 57.56; H, 6.11; N, 7.45.

15

Example 65

***N*-[1-(cyclohexylmethyl)-2-(1-ethylpropyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide**



20

Following the procedure for Example 14, using *N*-[1-(cyclohexylmethyl)-2-(1-ethylpropyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (85.4 mg, 0.194 mmol) (for preparation, see Example 7), sodium hydride (23.3 mg, 60%, 0.583 mmol) and iodomethane (82.6 mg, 0.582 mmol) in THF(10 mL). Yield: 69.9 mg (79%); white

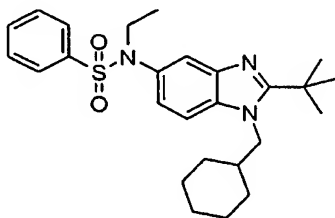
solid for TFA salt. ^1H NMR (400 MHz, CD_3OD): δ 0.95 (t, $J=7.42$ Hz, 6 H), 1.21 (m, 5 H), 1.61 (m, 2 H), 1.71 (m, 1 H), 1.76 (m, 2 H), 1.86 (m, 2 H), 1.99 (m, 3 H), 3.27 (s, 3 H), 3.38 (m, 1 H), 4.33 (d, $J=7.81$ Hz, 2 H), 7.29 (m, 1 H), 7.53 (m, 2 H), 7.57 (m, 3 H), 7.68 (m, 1 H), 7.83 (d, $J=8.98$ Hz, 1 H). MS (ESI) $(\text{M}+\text{H})^+ = 454.2$. Anal.

5 Calcd for $\text{C}_{26}\text{H}_{35}\text{N}_3\text{O}_2\text{S}+1.00$ TFA+0.20 H_2O (571.28): C, 58.87; H, 6.42; N, 7.36; Found: C, 58.85; H, 6.54; N, 7.24.

Example 66

N-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethylbenzenesulfonamide

10



Following the procedure for Example 14, using *N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]benzene sulfonamide (52.0 mg, 0.122 mmol) (for preparation, see Example 7), sodium hydride (20.3 mg, 60%, 0.508 mmol) and iodoethane (57.2

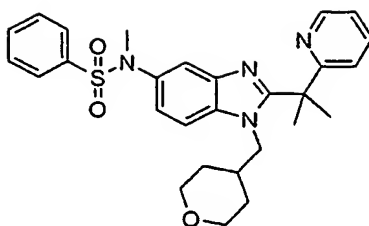
15 mg, 0.367 mmol) in THF (8 mL). Yield: 43.8 mg (79%), white solid for TFA salt. ^1H NMR (400 MHz, CD_3OD): δ 1.08 (t, $J=7.13$ Hz, 3 H), 1.25 (m, 5 H), 1.62 (m, 2 H), 1.67 (s, 9 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 2.10 (m, 1 H), 3.74 (q, $J=7.03$ Hz, 2 H), 4.45 (d, $J=7.62$ Hz, 2 H), 7.22 (dd, $J=8.98, 1.95$ Hz, 1 H), 7.49 (d, $J=1.56$ Hz, 1 H), 7.54 (m, 2 H), 7.60 (m, 2 H), 7.66 (m, 1 H), 7.85 (d, $J=8.98$ Hz, 1 H). MS (ESI)

20 $(\text{M}+\text{H})^+ = 454.0$. Anal. Calcd for $\text{C}_{26}\text{H}_{35}\text{N}_3\text{O}_2\text{S}+1.10$ TFA+0.20 H_2O (582.68): C, 58.13; H, 6.31; N, 7.21; Found: C, 58.15; H, 6.41; N, 6.99.

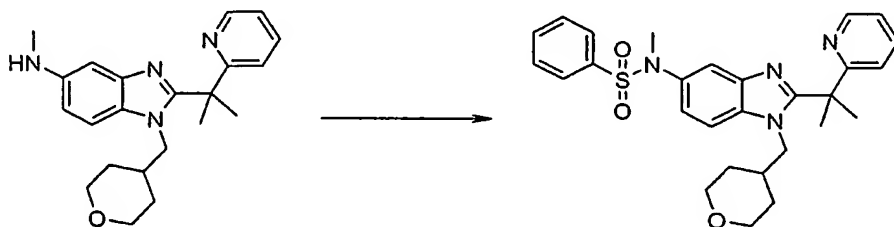
Example 67

N-methyl-*N*-[2-(1-methyl-1-pyridin-2-ylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide

25

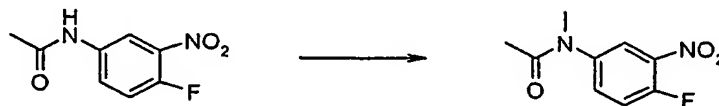


Step A. *N*-methyl-*N*-[2-(1-methyl-1-pyridin-2-ylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



- 5 *N*-methyl-2-(1-methyl-1-pyridin-2-ylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (85.0 mg, 0.13 mmol) (for preparation, see the following steps B, C, D, E, F, and G), DMAP (64.0 mg, 0.53 mmol) and benzenesulfonyl chloride (46.0 mg, 0.26 mmol) in MeCN (5 mL) were stirred for 8 h at room temperature. The reaction mixture was quenched with H₂O (3 mL). Upon
- 10 evaporation, the residue was purified by reversed-phase HPLC using 15-75% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 55.0 mg (68%). ¹HNMR (400 MHz, CD₃OD): δ 1.02 - 1.22 (m, 5 H), 2.01 (s, 6 H), 2.96 - 3.10 (m, 2 H), 3.28 (s, 3 H), 3.70 - 3.81 (m, 2 H), 3.93 (d, J=6.83 Hz, 2 H), 7.25 (dd, J=8.98, 2.15 Hz, 1 H), 7.39 - 7.47 (m, 1 H), 7.50 - 7.60 (m,
- 15 5 H), 7.64 - 7.76 (m, 4 H), 7.91 - 7.99 (m, 1 H). MS (ESI) (M+H)⁺ = 505.0. Anal. Calcd for C₂₈H₃₂N₄O₃S + 1.0 TFA + 0.2 H₂O + 0.4 CH₃OH (635.10): C, 57.49; H, 5.55; N, 8.82; Found: C, 57.52; H, 5.46; N, 8.72.

Step B. *N*-(4-fluoro-3-nitrophenyl)-*N*-methylacetamide

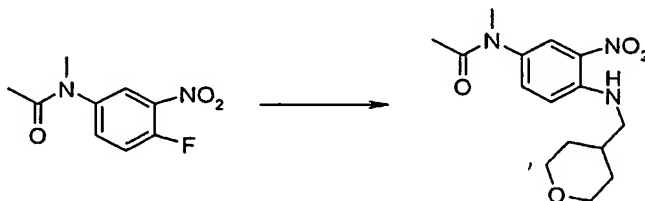


20

Sodium hydride (2.40g, 60%, 60 mmol) was added in portions to a solution of *N*-(4-fluoro-3-nitrophenyl)acetamide (7.93 g, 40 mmol) in THF (120 mL) at 0 °C. Stirring

for 20 min, iodomethane (17.0 g, 120 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, quenched with saturated NaHCO_3 (30 mL) and extracted with EtOAc (3x100 mL). The combined organic phases were washed with saturated NaCl (2x30 mL). After filtration and concentration, 8.73 g (100%) of the title compound was obtained as a brown solid. ^1H NMR (400 MHz, CDCl_3): δ 1.92 (s, 3 H), 3.30 (s, 3 H), 7.38 (s, 1 H), 7.52 (s, 1 H), 7.95 (s, 1 H).

Step C. *N*-methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide

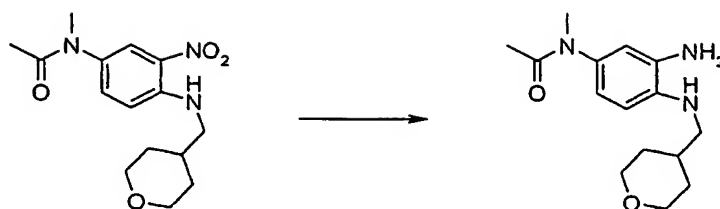


10

4-Aminomethylpyran (2.50 g, 21.7 mmol) was added to a mixture of *N*-(4-fluoro-3-nitrophenyl)-*N*-methylacetamide (4.61 g, 21.27 mmol) and sodium carbonate (5.10 g, 47.7 mmol) in EtOH (120 mL) at room temperature. The reaction mixture was heated for 3 days at 60 °C. Upon evaporation of ethanol, the residue was dissolved in EtOAc (400 mL), washed with H_2O (3x50 mL), saturated NaCl (3x50 mL), and dried over Na_2SO_4 . After filtration and concentration, 6.62 g (100%) of the title compound was obtained as an orange-red solid. ^1H NMR (400 MHz, CDCl_3): δ 1.38 - 1.52 (m, 2 H), 1.72 - 1.81 (m, 2 H), 1.90 (s, 3 H), 1.93 - 2.02 (m, 1 H), 3.23 (s, 3 H), 3.23 - 3.27 (m, 2 H), 3.36 - 3.49 (m, 2 H), 4.01 - 4.07 (m, 2 H), 6.91 (d, $J=9.18$ Hz, 1 H), 7.29 (dd, $J=9.08, 2.64$ Hz, 1 H), 8.05 (d, $J=2.34$ Hz, 1 H), 8.22 (t, $J=5.37$ Hz, 1 H). MS (ESI) $(\text{M}+\text{H})^+ = 309.12$.

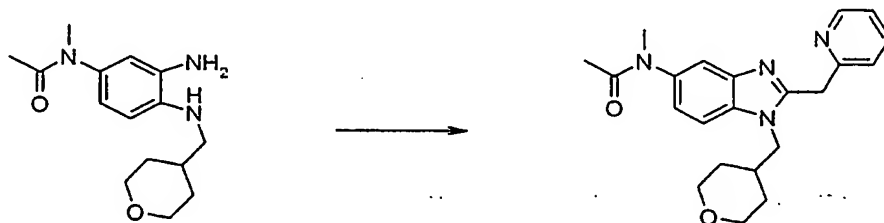
20

Step D. *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide



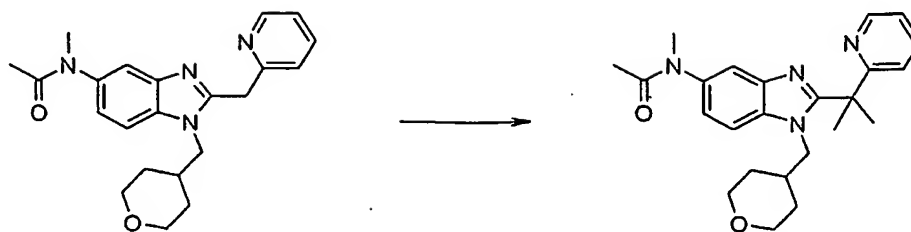
- N*-methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (5.39 g, 16.7 mmol) was hydrogenated in ethyl acetate (200 mL) catalyzed by 10% Pd/C (0.2 g) at 30-40 psi H₂ in Parr shaker for 18 h at room temperature. After
- 5 filtration through celite and concentration, 6.0 g (100%) of a purple solid was obtained as HCl salt, which was used in the next step without purification. ¹H NMR (400 MHz, CD₃OD): δ 1.32 - 1.46 (m, 2 H), 1.78 - 1.84 (m, 2 H), 1.85 (s, 3 H), 1.91 - 2.06 (m, 1 H), 3.16 (d, *J*=6.83 Hz, 2 H), 3.20 (s, 3 H), 3.39 - 3.51 (m, 2 H), 3.94 - 4.03 (m, 2 H), 7.01 (d, *J*=8.59 Hz, 1 H), 7.12 (d, *J*=2.15 Hz, 1 H), 7.17 (dd, *J*=8.49, 4.39
- 10 Hz, 1 H), MS (ESI) (*M*+*H*)⁺: 278.7

Step E. *N*-methyl-*N*-[2-(pyridin-2-ylmethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide



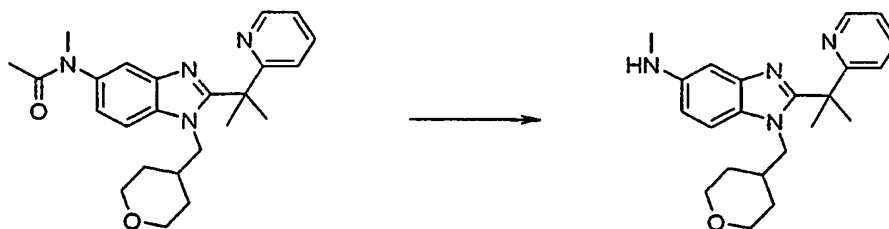
- 15 Following the procedure for Example 10, using *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide hydrochloride (416.1 mg, 1.33 mmol), 2-pyridylacetic acid hydrochloride (286.4 mg, 1.65 mmol), diisopropylethylamine (970 mg, 7.5 mmol) and HATU (680.0 mg, 1.80 mmol) in DMF (15 mL) and then in acetic acid (10 mL), the crude product was purified by MPLC using EtOAc/MeOH
- 20 (20:1) on silica gel to give 308.1 mg (61%) of a yellow solid as the title compound. MS (ESI) (*M*+*H*)⁺ = 379.0.

Step F. *N*-methyl-*N*-[2-(1-methyl-1-pyridin-2-ylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide



KHMDS (1.6 mL, 0.5 M, 0.8 mmol) was added to a solution of *N*-methyl-*N*-[2-(pyridin-2-ylmethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide (248.4 mg, 0.656 mmol) in THF (25 mL) at -78 °C. Stirring for 10 min, iodomethane (113.6 mg, 50 uL, 0.80 mmol) was added. The mixture was stirred for 30 min at -78 °C and 30 min at room temperature, then cooled down to -78 °C again. Another 1.2 equivalent KHMDS and iodomethane were added. The resulting mixture was stirred for 30 min at -78 °C and 45 min at room temperature, quenched with saturated NaHCO₃ (5 mL), and extracted with EtOAc (3x20 mL). The combined organic phases were washed with saturated NaHCO₃ (20 mL), saturated NaCl (20 mL) and dried over Na₂SO₄. After filtration and concentration, the residue was purified by MPLC using EtOAc/MeOH (20:1) on silica gel to give 218.1 mg (90%) of the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 1.02 - 1.12 (m, 2 H), 1.13 - 1.19 (m, 2 H), 1.19 - 1.27 (m, 1 H), 1.90 (s, 3 H), 1.97 (s, 6 H), 2.90 - 3.11 (m, 2 H), 3.31 (s, 3 H), 3.68 (d, *J*=7.22 Hz, 2 H), 3.81 (m, 2 H), 7.04 (dd, *J*=8.49, 2.05 Hz, 1 H), 7.18 - 7.32 (m, 3 H), 7.57 - 7.70 (m, 2 H), 8.53 - 8.70 (m, 1 H). MS (ESI) (M+H)⁺ = 407.03.

Step G. *N*-methyl-2-(1-methyl-1-pyridin-2-ylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine

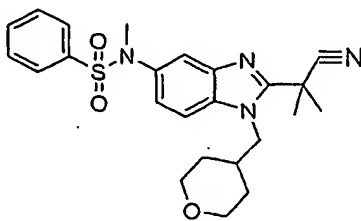


N-methyl-*N*-[2-(1-methyl-1-pyridin-2-ylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide (214.0 mg, 0.526 mmol) was dissolved in 5 mL of

EtOH-2*N* HCl (3:2), and then heated at 120°C in a Personal Chemistry SmithSynthesizer microwave instrument for 1h. After concentration and dried *in vacuo*, 331 mg (100%) of a grey white solid was obtained as the title product. ¹H NMR (400 MHz, DMSO-*D*₆): δ 0.86 - 1.08 (m, 4 H), 1.94 (s, 6 H), 1.96 - 2.03 (m, 1 H), 2.71 - 2.92 (m, 5 H), 3.55 - 3.70 (m, 2 H), 3.86 (d, *J*=5.47 Hz, 2 H), 7.31 - 7.48 (m, 2 H), 7.69 (d, *J*=7.42 Hz, 1 H), 7.74 - 7.84 (m, 1 H), 7.93 (t, *J*=8.30 Hz, 1 H), 8.48 (d, *J*=4.10 Hz, 2 H). MS (ESI) (*M*+*H*)⁺ = 365.04.

Example 68

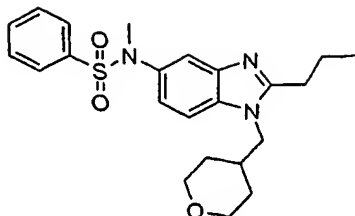
- 10 *N*-[2-(1-cyano-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



- Following the procedure for Example 10, using *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide (1.0 g, 2.66 mmol) (for preparation, see the steps B and C in Example 41), 2-cyano-2-methylpropanoic acid (0.33 g, 2.93 mmol), diisopropylethylamine (0.76 g, 5.85 mmol) and HATU (1.21 g, 3.19 mmol) in DMF (30 mL) and then in acetic acid (50 mL), the crude product was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 0.41 g (34%) of a white solid as the title compound. ¹H NMR (400 MHz, CD₃OD): δ 1.43 - 1.53 (m, 2 H), 1.54 - 1.67 (m, 2 H), 1.93 (s, 6 H), 2.38 - 2.55 (m, 1 H), 3.24 (s, 3 H), 3.32 - 3.40 (m, 2 H), 3.93 (m, 2 H), 4.44 (d, *J*=7.62 Hz, 2 H), 7.13 (dd, *J*=8.79, 2.15 Hz, 1 H), 7.32 (d, *J*=1.56 Hz, 1 H), 7.47 - 7.57 (m, 4 H), 7.62 (d, *J*=8.98 Hz, 1 H), 7.64 - 7.69 (m, 1 H). MS (ESI) (*M*+*H*)⁺ = 453.0. Anal. Calcd for C₂₄H₂₈N₄O₃S + 0.8 TFA + 0.2 H₂O (547.40): C, 56.17; H, 5.38; N, 10.24; Found: C, 56.05; H, 5.29; N, 10.44.

Example 69

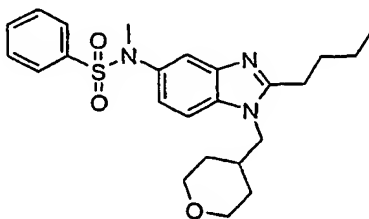
N-methyl-*N*-[2-propyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



Following the procedure for Example 10, using *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide (75.3 mg, 0.20 mmol) (for
 5 preparation, see the steps B and C in Example 41), butyric acid (18.5 mg, 0.21 mmol), diisopropylethylamine (56.9 mg, 0.44 mmol) and HATU (91.3 mg, 0.24 mmol) in DMF (5 mL) and then in acetic acid (5 mL), the crude product was purified by reversed-phase HPLC using 20-50% CH₃CN/H₂O and then lyophilized affording
 10 the title compound as the corresponding TFA salt. Yield: 60.5 mg (71%). ¹HNMR (400 MHz, CD₃OD): δ 1.14 (t, J=7.42 Hz, 3 H), 1.43 - 1.65 (m, 4 H), 1.88 - 2.04 (m, 2 H), 2.15 - 2.35 (m, 1 H), 3.16 - 3.24 (m, 2 H), 3.27 (s, 3 H), 3.31 - 3.42 (m, 2 H), 3.88 - 3.99 (m, 2 H), 4.36 (d, J=7.62 Hz, 2 H), 7.31 (dd, J=8.98, 1.95 Hz, 1 H), 7.47 - 7.59 (m, 5 H), 7.63 - 7.73 (m, 1 H), 7.86 (d, J=8.98 Hz, 1 H). MS (ESI) (M+H)⁺ =
 15 428.0. Anal. Calcd for C₂₃H₂₉N₃O₃S+ 1.80 TFA+2.3 H₂O +0.60 CH₃CN (698.88): C, 47.78; H, 5.37; N, 7.21; Found: C, 47.76; H, 5.38; N, 7.20.

Example 70

N-[2-butyl-1-((tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-
 20 methylbenzenesulfonamide

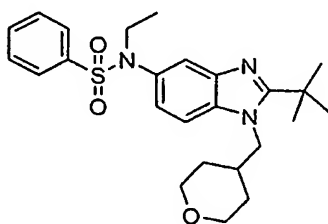


Following the procedure for Example 10, using *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide (75.3 mg, 0.20 mmol) (for
 25 preparation, see the steps B and C in Example 41), pentanoic acid (21.5 mg, 0.21 mmol), diisopropylethylamine (56.9 mg, 0.44 mmol) and HATU (91.3 mg, 0.24

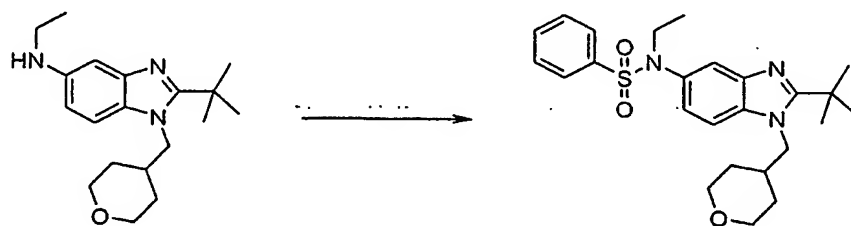
mmol) in DMF (5 mL) and then in acetic acid (5 mL), the crude product was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 56.4 mg (64%) of a white solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 1.05 (t, J=7.32 Hz, 3 H), 1.45 - 1.63 (m, 6 H), 1.85 - 1.99 (m, 2 H), 2.15 - 2.32 (m, 1 H), 3.20 - 3.26 (m, 2 H), 3.27 (s, 3 H), 3.31 - 3.41 (m, 2 H), 3.85 - 4.05 (m, 2 H), 4.37 (d, J=7.62 Hz, 2 H), 7.32 (dd, J=8.98, 1.95 Hz, 1 H), 7.47 - 7.60 (m, 5 H), 7.63 - 7.73 (m, 1 H), 7.87 (d, J=8.79 Hz, 1 H). MS (ESI) (M+H)⁺ = 442.0. Anal. Calcd for C₂₄H₃₁N₃O₃S+ 1.00 HCl+1.00 H₂O (496.07): C, 58.11; H, 6.91; N, 8.47; Found: C, 58.14 ; H, 6.92; N, 8.30.

10 Example 71

N-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethylbenzenesulfonamide



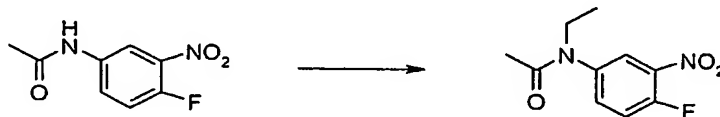
Step A. *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethylbenzenesulfonamide



2-*tert*-butyl-*N*-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (52.8 mg, 0.15 mmol) (for preparation, see the following steps B, C, D, E and F), DMAP (73.3 mg, 0.60 mmol) and benzenesulfonyl chloride (53.0 mg, 0.30 mmol) in MeCN (5 mL) were stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (100 mL), washed with saturated NaHCO₃ (10 mL) and saturated NaCl (10 mL) and dried over Na₂SO₄. Upon evaporation, the residue was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 53.0 mg (77%) of a white solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 0.95 (t, J=7.03

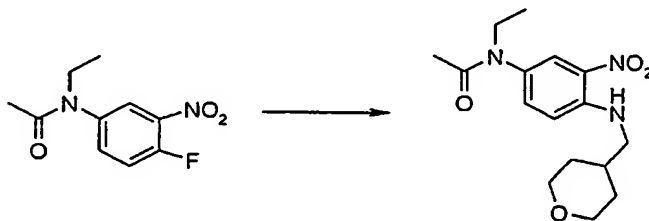
- Hz, 3 H), 1.36 - 1.50 (m, 4 H), 1.53 (s, 9 H), 2.08 - 2.29 (m, 1 H), 3.12 - 3.27 (m, 2 H), 3.65 (q, J=7.09 Hz, 2 H), 3.76 - 3.88 (m, 2 H), 4.37 (d, J=7.03 Hz, 2 H), 7.03 (d, J=8.79 Hz, 1 H), 7.32 (s, 1 H), 7.51 - 7.63 (m, 4 H), 7.64 - 7.76 (m, 1 H), 7.83 (d, J=8.59 Hz, 1 H). MS (ESI) (M+H)⁺ = 456.0. Anal. Calcd for C₂₅H₃₃N₃O₃S + 1.20
- 5 TFA+0.3 CH₃CN (604.77): C, 55.61; H, 5.85; N, 7.64; Found: C, 55.57; H, 5.79; N, 7.61.

Step B. *N*-ethyl-*N*-(4-fluoro-3-nitrophenyl)acetamide



- 10 Sodium hydride (1.20g, 60%, 30 mmol) was added in portions to a solution of *N*-(4-fluoro-3-nitrophenyl)acetamide (3.96 g, 20 mmol) (for preparation see the step B in Example 47) in THF (100 mL) at 0 °C. Stirring for 20 min, iodoethane (9.32 g, 60 mmol) was added. The reaction mixture was stirred overnight at room temperature, quenched with saturated NaHCO₃ (30 mL) and extracted with EtOAc (3x100 mL).
- 15 The combined organic phases were washed with saturated NaCl (2x30 mL). After filtration and concentration, the residue was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 2.36 g (52%) of a yellow solid as the title compound. ¹H NMR (400 MHz, CDCl₃): δ 1.14 (t, J=6.93 Hz, 3 H), 1.88 (s, 3 H), 3.70 - 3.84 (q, J=7.0 Hz, 2 H), 7.34 - 7.43 (m, 1 H), 7.48 (s, 1 H), 7.87 - 7.98 (m, 1 H).
- 20

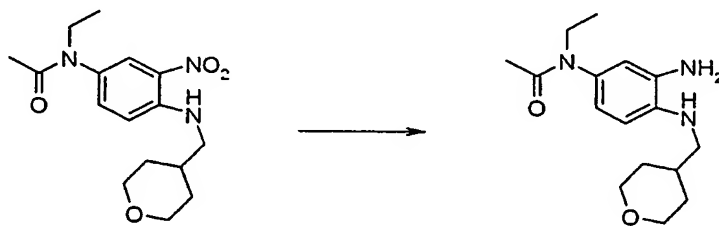
Step C. *N*-ethyl-*N*-(3-nitro-4-[(tetrahydro-2*H*-pyran-4-yl)methyl]amino]phenyl)acetamide



- 4-Aminomethylpyran (1.32 g, 11.4 mmol) was added to a mixture of *N*-ethyl-*N*-(4-fluoro-3-nitrophenyl)acetamide (2.36 g, 10.4 mmol) and sodium carbonate (2.43 g, 22.9 mmol) in EtOH (70 mL) at room temperature. The reaction mixture was heated
- 25

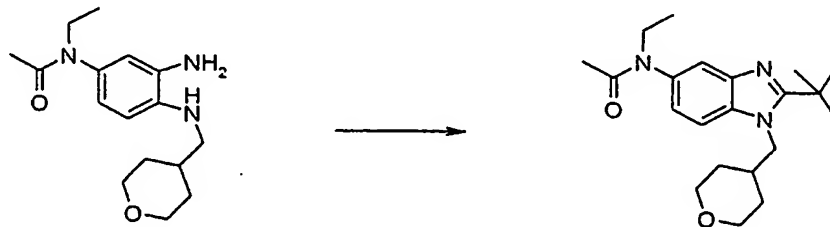
for a weekend at 60 °C. Upon evaporation of ethanol, the residue was diluted with H₂O (50 mL), and extracted with EtOAc (3x100 mL). The combined organic phases were washed saturated NaCl (2x50 mL) and dried over Na₂SO₄. After filtration and concentration, the residue was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 2.83 g (85%) of an orange-red solid as the title compound. ¹H NMR (400 MHz, CDCl₃): δ 1.11 (t, *J*=7.13 Hz, 3 H), 1.38 - 1.52 (m, 2 H), 1.78 (m, 2 H), 1.86 (s, 3 H), 1.92 - 2.04 (m, 1 H), 3.20 - 3.29 (m, 2 H), 3.39 - 3.49 (m, 2 H), 3.71 (q, *J*=7.09 Hz, 2 H), 4.00 - 4.08 (m, 2 H), 6.91 (d, *J*=8.98 Hz, 1 H), 7.24 (d, *J*=2.54 Hz, 1 H), 8.01 (d, *J*=2.54 Hz, 1 H), 8.22 (t, *J*=4.98 Hz, 1 H).

Step D. *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-ethylacetamide



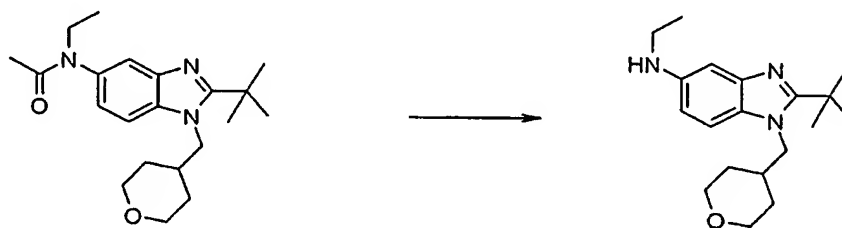
N-ethyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (2.83 g, 8.79 mmol) was hydrogenated in ethyl acetate (200 mL) catalyzed by 10% Pd/C (0.2 g) at 30-40 psi H₂ in Parr shaker for 16 h at room temperature. After filtration through celite and concentration, 2.45 g (95%) of a light yellow solid was obtained, which was used in the next step without purification. MS (ESI) (M+H)⁺ = 292.3

Step E. *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethylacetamide



Following the procedure for Step A in Example 7, using *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-ethylacetamide (803.1 mg, 2.75 mmol), DMAP (671.9 mg, 5.50 mmol) and trimethylacetyl chloride (380.9 mg, 3.16 mmol) in CH₂Cl₂ (60 mL) and then in DCE (30 mL), the crude product was purified by MPLC using EtOAc/MeOH (20:1) on silica gel. Yield: 694.1 mg (71%). ¹H NMR (400 MHz, CDCl₃): δ 1.12 (t, *J*=7.13 Hz, 3 H), 1.51 - 1.57 (m, 4 H), 1.58 (s, 9 H), 1.83 (s, 3 H), 2.21 - 2.40 (m, 1 H), 3.26 - 3.43 (m, 2 H), 3.78 (q, *J*=7.23 Hz, 2 H), 3.94 - 4.07 (m, 2 H), 4.22 (d, *J*=7.42 Hz, 2 H), 7.02 (dd, *J*=8.59, 1.95 Hz, 1 H), 7.34 (d, *J*=8.59 Hz, 1 H), 7.54 (d, *J*=0.98 Hz, 1 H). MS (ESI) (M+H)⁺ = 358.07.

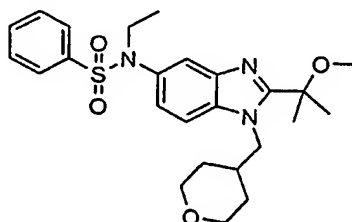
Step F. 2-*tert*-butyl-*N*-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine



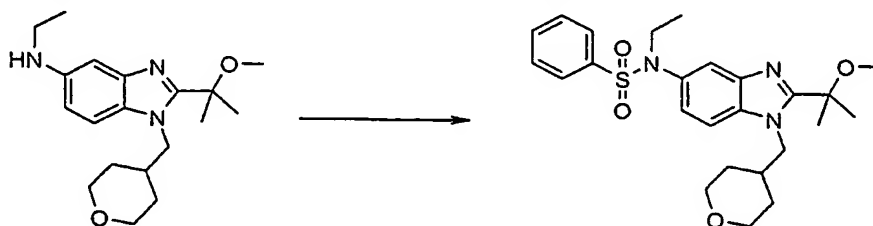
N-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethylacetamide (648.3 mg, 2.06 mmol) was dissolved in 15 mL of EtOH-2*N* HCl (3:2), and then heated at 120°C in a Personal Chemistry SmithSynthesizer microwave instrument for 3h. After concentration and dried *in vacuo*, 754.71 mg (100%) of a grey white solid was obtained as the title product. MS (ESI) (M+H)⁺ = 316.3.

Example 72

***N*-ethyl-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide**

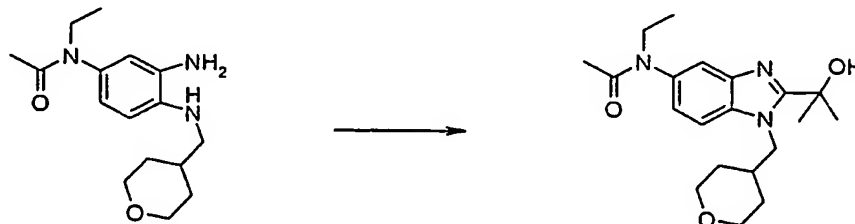


Step A *N*-ethyl-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



- 5 Following the procedure for the step A in Example 71, using *N*-ethyl-2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (50.0 mg, 0.136 mmol) (for preparation, see the following steps B, C and D), DMAP (64.5 mg, 0.50 mmol) and benzenesulfonyl chloride (45.9.0 mg, 0.26 mmol) in MeCN (5 mL), the crude product was purified by reversed-phase HPLC
- 10 using 20-50% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 12.1 mg (19%). ¹HNMR (400 MHz, CD₃OD): δ 1.07 (t, J=7.13 Hz, 3 H), 1.48 - 1.58 (m, 4 H), 1.78 (s, 6 H), 2.27 - 2.51 (m, 1 H), 3.32 (s, 3 H), 3.33 - 3.40 (m, 2 H), 3.72 (q, J=7.23 Hz, 2 H), 3.88 - 4.00 (m, 2 H), 4.51 (d, J=7.42 Hz, 2 H), 7.15 (dd, J=8.88, 1.86 Hz, 1 H), 7.40 (d, J=1.76 Hz, 1 H), 7.49 - 7.58
- 15 (m, 2 H), 7.59 - 7.64 (m, 2 H), 7.63 - 7.70 (m, 1 H), 7.76 (d, J=8.98 Hz, 1 H). MS (ESI) (M+H)⁺ = 472.0. Anal. Calcd for C₂₅H₃₃N₃O₄S + 0.90 TFA + 0.20 H₂O + 0.40 CH₃OH (590.66): C, 55.31; H, 6.13; N, 7.11; Found: C, 55.29; H, 6.06; N, 7.10.

Step B. *N*-ethyl-*N*-[2-(1-hydroxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide

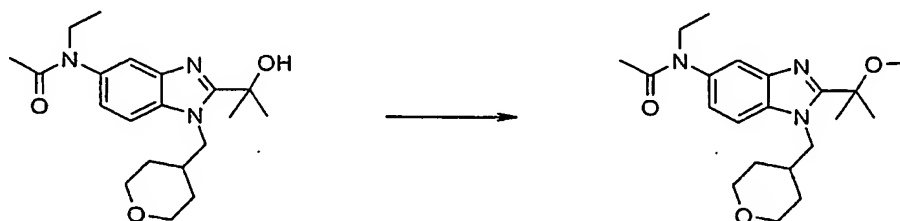


Following the procedure for Example 10, using *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-ethylacetamide (0.841 g, 2.88 mmol) (for preparation, see the steps B, C and D in Example 71), 2-hydroxy-2-methylpropanoic acid (0.330 g,

3.17 mmol), diisopropylethylamine (0.558 g, 4.32 mmol) and HATU (1.31 g, 3.46 mmol) in DMF (40 mL) and then in acetic acid (50 mL), the crude product (1.78 g, purity >43%) was used directly for next step without purification. MS (ESI) (M+H)⁺ = 360.04.

5

Step C. *N*-ethyl-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide

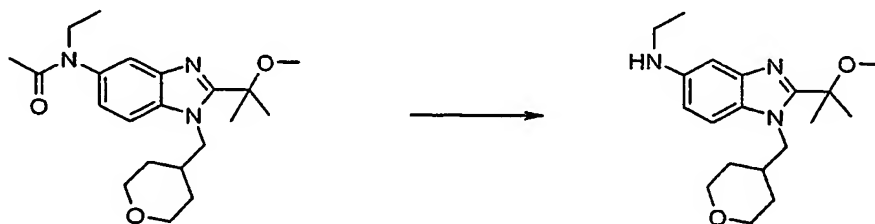


Sodium hydride (0.35 g, 60%, 8.64 mmol) was added in portions to a solution of *N*-ethyl-*N*-[2-(1-hydroxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide (1.78 g of the above crude product, 2.88 mmol) in THF (100 mL) at 0 °C. Stirring for 20 min, iodoethane (1.23 g, 8.64 mmol) was added. The reaction mixture was stirred overnight at room temperature, quenched with saturated NH₄Cl (20 mL) and diluted with EtOAc (100 mL), washed with saturated NaCl (2x20 mL). After filtration and concentration, the residue was purified by MPLC using EtOAc/MeOH (20:1) on silica gel to give 0.423 g (39%) of a grey white solid as the title compound. MS (ESI) (M+H)⁺ = 374.03.

15

Step D. *N*-ethyl-2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine

20



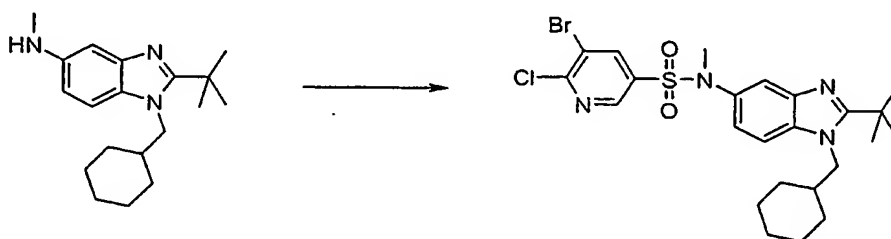
N-ethyl-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide (422.5 mg, 1.13 mmol) was dissolved in 15 mL of

EtOH-2*N* HCl (3:2), and then heated at 120°C in a Personal Chemistry SmithSynthesizer microwave instrument for 3.5 h. After concentration and dried *in vacuo*, 441.9 mg (100%) of a light brown solid was obtained as the title product. MS (ESI) (M+H)⁺ = 332.04.

5

Example 73

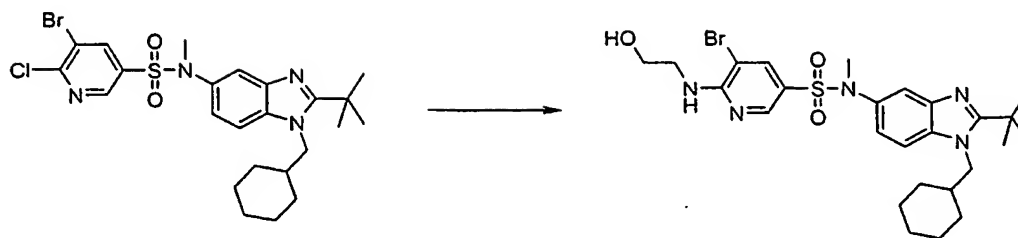
5-Bromo-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-6-chloro-*N*-methylpyridine-3-sulfonamide



- 10 2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (for preparation, see Example 1) (80 mg, 0.267 mmol) and 3-bromo-2-chloro pyridine-5-sulphonyl chloride (95 mg, 0.320 mmol) were stirred in 3 mL of DCM containing a catalytic amount of DMAP at rt overnight. The solution was washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude
- 15 product was purified by silica gel flash chromatography using 2:1 / hexanes:EtOAc as eluent. Yield: 127 mg (86%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.09 (m, 1 H), 1.11 (m, 1 H), 1.15 (m, 1 H), 1.18 (m, 1 H), 1.20 (m, 1 H), 1.54 (s, 9 H), 1.64 (m, 1 H), 1.67 (m, 1 H), 1.70 (m, 1 H), 1.75 (m, 2 H), 2.02 (m, 1 H), 3.29 (s, 3 H), 4.13 (d, J=7.42 Hz, 2 H), 7.12 (dd, J=8.79, 1.56 Hz, 1 H), 7.31 (m, 2 H), 8.06 (d, J=2.15 Hz, 1 H), 8.41 (d, J=2.15 Hz, 1 H); MS (ESI) (M+H)⁺: 553.0; Anal. Calcd for C₂₄H₃₀N₄O₂SClBr + 0.1 H₂O: C, 51.87; H, 5.48; N, 10.08. Found: C, 52.01; H, 5.54; N, 9.83.
- 20

Example 74

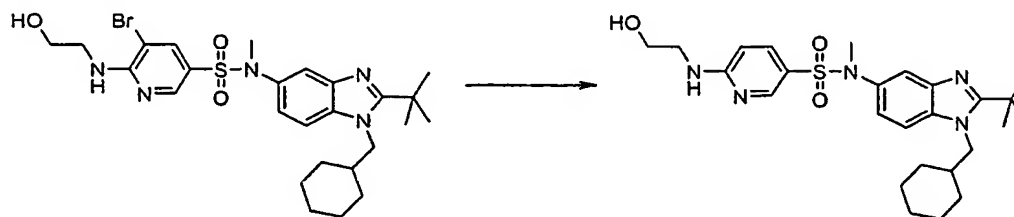
- 25 **5-Bromo-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-6-[(2-hydroxyethyl)amino]-*N*-methylpyridine-3-sulfonamide**



5-Bromo-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-6-chloro-*N*-methylpyridine-3-sulfonamide (50 mg, 0.0903 mmol) and ethanolamine (0.025 mL, 0.451 mmol) were dissolved in 2 mL of DMF. The solution was heated at 120°C for 30 min using a Personal Chemistry microwaves instrument. The solvent was evaporated. The product was directly purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 45 mg (72%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.25 (m, 5 H), 1.65 (m, 2 H), 1.68 (s, 9 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 3.27 (s, 3 H), 3.61 (t, *J*=5.37 Hz, 2 H), 3.70 (t, *J*=5.47 Hz, 2 H), 4.47 (d, *J*=7.62 Hz, 2 H), 7.38 (dd, *J*=9.08, 2.05 Hz, 1 H), 7.61 (d, *J*=2.15 Hz, 1 H), 7.63 (d, *J*=1.56 Hz, 1 H), 7.89 (d, *J*=8.98 Hz, 1 H), 8.09 (d, *J*=2.15 Hz, 1 H); MS (ESI) (*M*+*H*)⁺ 578.3; Anal. Calcd for C₂₆H₃₈N₅O₃SBr + 1.9 TFA + 0.2 H₂O: C, 44.69; H, 5.07; N, 8.74. Found: C, 44.71; H, 5.13; N, 8.74.

Example 75

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-6-[(2-hydroxyethyl)amino]-*N*-methylpyridine-3-sulfonamide

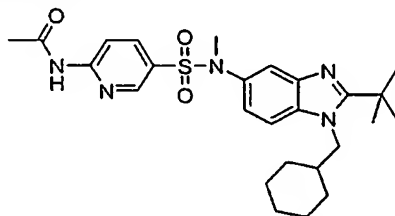


5-Bromo-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-6-[(2-hydroxyethyl)amino]-*N*-methylpyridine-3-sulfonamide (55 mg, 0.0794 mmol) was dissolved in 15 mL of EtOH containing a catalytic amount of 10% Pd/C. The solution was shaken under H₂ atmosphere (45 psi) using a Parr hydrogenation apparatus at rt

for 5h. The solution was filtered through celite and the solvent was evaporated. The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 31 mg (64%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.24 (m, 5 H), 1.64 (m, 2 H), 1.68 (s, 9 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 2.12 (m, 1 H), 3.27 (s, 3 H), 3.49 (t, J=5.57 Hz, 2 H), 3.70 (t, J=5.57 Hz, 2 H), 4.47 (d, J=7.62 Hz, 2 H), 6.63 (d, J=9.18 Hz, 1 H), 7.41 (dd, J=8.98, 1.95 Hz, 1 H), 7.47 (d, J=7.42 Hz, 1 H), 7.61 (d, J=1.95 Hz, 1 H), 7.88 (d, J=8.98 Hz, 1 H), 8.01 (d, J=2.34 Hz, 1 H); MS (ESI) (M+H)⁺: 500.3; Anal. Calcd for C₂₆H₃₇N₅O₃S + 2.5 TFA + 1.7 H₂O: C, 45.67; H, 5.30; N, 8.59. Found: C, 45.69; H, 5.32; N, 8.43.

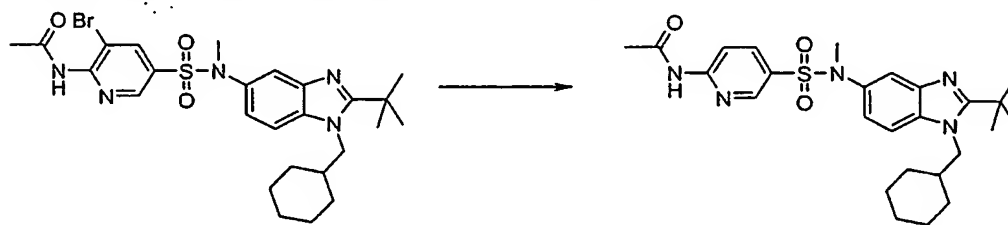
Example 76

N-(5-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}pyridin-2-yl)acetamide



15

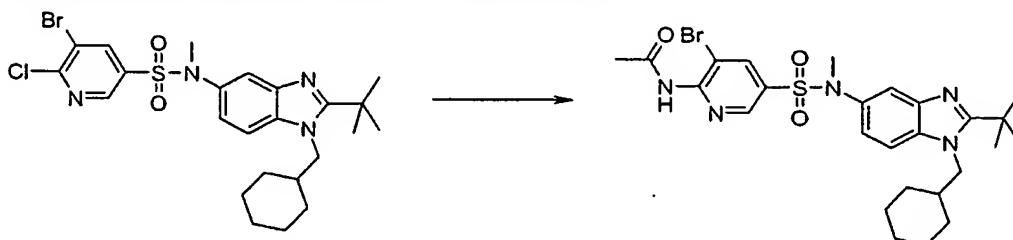
Step A. *N*-(5-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}pyridin-2-yl)acetamide



Following the same procedure as in Example 74 using *N*-(3-bromo-5-{[[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}pyridin-2-yl)acetamide (see Step B for preparation) (16 mg, 0.0278 mmol). The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 13 mg (76%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.24 (m, 5 H), 1.64 (m, 2 H), 1.67 (s, 9 H),

1.70 (m, 1 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 2.19 (s, 3 H), 3.30 (m, 3 H), 4.46 (d, J=7.62 Hz, 2 H), 7.36 (dd, J=8.98, 2.15 Hz, 1 H), 7.58 (d, J=1.95 Hz, 1 H), 7.81 (dd, J=8.89, 2.25 Hz, 1 H), 7.87 (d, J=8.98 Hz, 1 H), 8.25 (d, J=8.98 Hz, 1 H), 8.40 (s, 1 H); MS (ESI) (M+H)⁺: 498.2; Anal. Calcd for C₂₆H₃₅N₅O₃S + 2.0 TFA + 1.0 H₂O: C, 48.45; H, 5.29; N, 9.42. Found: C, 48.37; H, 5.16; N, 9.64.

Step B. *N*-(3-Bromo-5-[[[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]pyridin-2-yl)acetamide



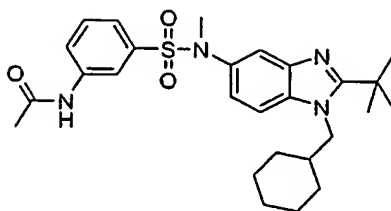
10

5-Bromo-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-6-chloro-*N*-methylpyridine-3-sulfonamide (87 mg, 0.157 mmol) was dissolved in 2 mL of DMF containing ammonia (28% w/v in water) (1 mL). The solution was heated at 120°C for 30 min using a Personal Chemistry microwaves instrument. The solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. The product was dissolved in 2 mL of DCE containing a catalytic amount of DMAP. Acetyl chloride (0.055 mL, 0.785 mmol) was added and the solution was heated at 120°C for 30 min using a Personal Chemistry microwaves instrument. The solution was washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes:EtOAc as eluent. Yield: 16 mg (18%); MS (ESI) (M+H)⁺: 578.28.

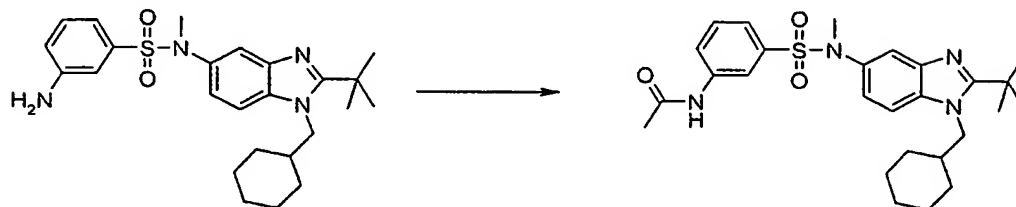
25

Example 77

N-(3-[[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl)acetamide

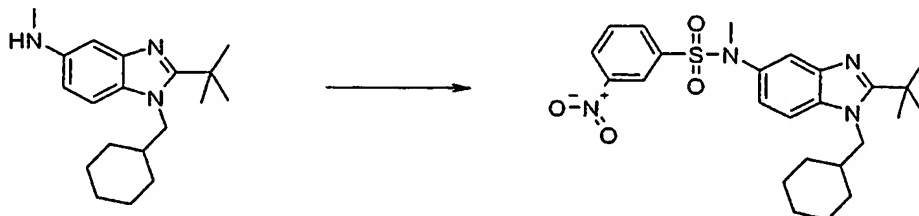


Step A. *N*-(3-[[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl)acetamide



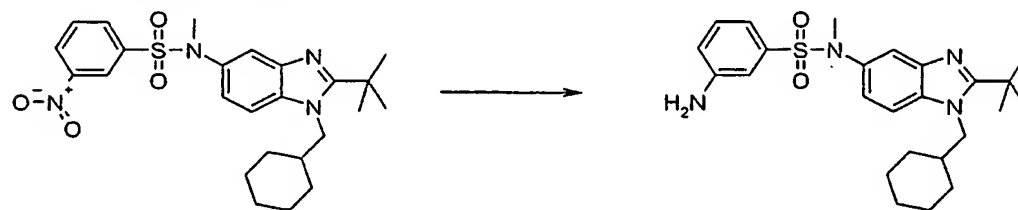
- 5 3-Amino-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (see Step B and C for preparation) (40 mg, 0.0880 mmol) and acetyl chloride (0.008 mL, 0.106 mmol) were stirred in 2 mL of DCM containing a catalytic amount of DMAP at rt for 1h. The solvent was evaporated.
- The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and
- 10 lyophilized affording the title compound as the corresponding TFA salt. Yield: 38 mg (71%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.24 (m, 5 H), 1.65 (m, 2 H), 1.68 (s, 9 H), 1.71 (m, 1 H), 1.77 (m, 2 H), 2.07 (s, 3 H), 2.11 (m, 1 H), 3.28 (s, 3 H), 4.46 (d, J=7.42 Hz, 2 H), 7.32 (m, 2 H), 7.47 (t, J=8.01 Hz, 1 H), 7.59 (m, 2 H), 7.84 (d, J=8.98 Hz, 1 H), 7.93 (t, J=1.86 Hz, 1 H); MS (ESI) (M+H)⁺: 497.2; Anal. Calcd for
- 15 C₂₇H₃₆N₄O₃S + 1.7 TFA + 0.5 H₂O: C, 52.20; H, 5.58; N, 8.01. Found: C, 52.14; H, 5.48; N, 8.08.

Step B. *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-3-nitrobenzenesulfonamide



2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (50 mg, 0.167 mmol) and 3-nitrophenylsulfonyl chloride (44 mg, 0.200 mmol) were stirred in 3 mL of DCM containing a catalytic amount of DMAP at rt overnight. The solution was washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes:EtOAc as eluent. Yield: 75 mg (94%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.09 (m, 1 H), 1.11 (m, 1 H), 1.15 (m, 1 H), 1.18 (m, 1 H), 1.21 (m, 1 H), 1.53 (s, 9 H), 1.64 (m, 1 H), 1.67 (m, 1 H), 1.72 (m, 1 H), 1.76 (m, 1 H), 2.03 (m, 1 H), 3.29 (s, 3 H), 4.12 (d, J=7.62 Hz, 2 H), 7.18 (m, 2 H), 7.31 (d, J=8.40 Hz, 1 H), 7.67 (t, J=8.01 Hz, 1 H), 7.91 (m, 1 H), 8.39 (t, J=1.76 Hz, 1 H), 8.43 (ddd, J=8.10, 2.25, 0.98 Hz, 1 H).

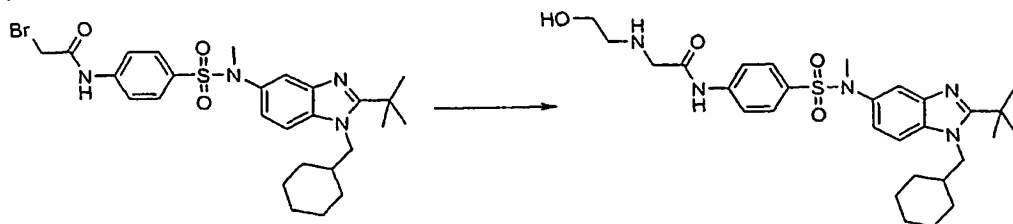
Step C. 3-Amino-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-3-nitrobenzenesulfonamide (72 mg, 0.149 mmol) was dissolved in 15 mL of EtOH containing a catalytic amount of 10% Pd/C. The solution was shaken under H₂ atmosphere (45 psi) using a Parr hydrogenation apparatus at rt for 6h. The solution was filtered through celite and the solvent was evaporated. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes:EtOAc as eluent. Yield: 43 mg (63%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.08 (m, 1 H), 1.11 (m, 1 H), 1.15 (m, 1 H), 1.18 (m, 1 H), 1.20 (m, 1 H), 1.54 (s, 9 H), 1.65 (m, 1 H), 1.68 (m, 1 H), 1.71 (m, 1 H), 1.75 (m, 2 H), 2.03 (m, 1 H), 3.22 (s, 3 H), 3.82 (m, 2 H), 4.11 (d, J=7.42 Hz, 2 H), 6.83 (ddd, J=8.01, 2.44, 0.88 Hz, 1 H), 6.90 (t, J=1.95 Hz, 1 H), 6.97 (m, 1 H), 7.22 (m, 2 H), 7.28 (m, 1 H), 7.33 (m, 1 H).

Example 78

*N*¹-(4-[[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]](methylamino)sulfonyl]phenyl)-*N*²-(2-hydroxyethyl)glycinamide



5

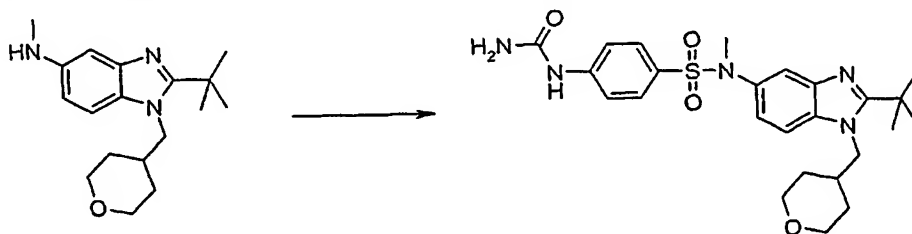
2-Bromo-*N*-(4-[[[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]](methylamino)sulfonyl]phenyl)acetamide (for preparation, see Example 33, Step B) (56 mg, 0.0973 mmol) and ethanolamine (0.030 mL, 0.487 mmol) were heated in 1 mL of DMF at 125°C for 15 min using a Personal Chemistry microwaves instrument.

10 The solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. The product was purified by reversed-phase HPLC using 10-70% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 20 mg (31%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.24 (m, 5 H), 1.63 (m, 2 H), 1.67 (s, 9 H), 1.70 (m, 1 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 3.24 (m, 2 H), 3.27 (s, 3 H), 3.85 (m, 2 H), 4.07 (s, 2 H), 4.45 (d, J=7.62 Hz, 2 H), 7.31 (dd, J=9.08, 2.05 Hz, 1 H), 7.53 (d, J=8.98 Hz, 2 H), 7.59 (d, J=1.76 Hz, 1 H), 7.77 (d, J=8.98 Hz, 2 H), 7.84 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 556.3.

20

Example 79

4-[(Aminocarbonyl)amino]-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide

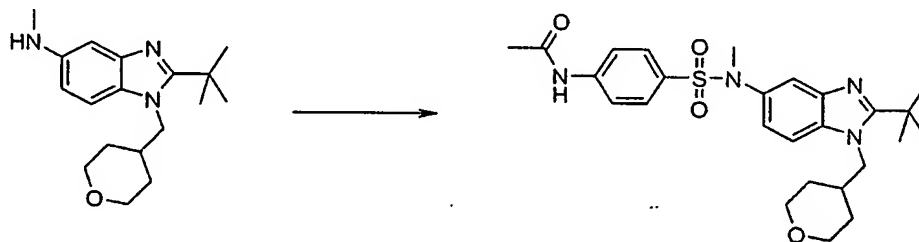


2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (see Example 50 for preparation) (30 mg, 0.0995 mmol) and 4-ureido-benzenesulfonyl chloride (28 mg, 0.119 mmol) were stirred in 3 mL of DMF containing a catalytic amount of DMAP at rt for 4h. The solvent was evaporated.

- 5 The product was purified by reversed-phase HPLC using 10-70% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 24 mg (39%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.50 - 1.55 (m, 2 H), 1.56 - 1.63 (m, 2 H), 1.67 (s, 9 H), 2.32 - 2.40 (m, 1 H), 3.23 (s, 3 H), 3.34 (dt, J=11.42, 2.34 Hz, 2 H), 3.92 (d, J=3.12 Hz, 1 H), 3.95 (d, J=3.12 Hz, 1 H), 4.51 (d, J=7.42 Hz, 2 H),
 10 7.32 (ddd, J=9.03, 2.00, 0.88 Hz, 1 H), 7.38 (d, J=8.20 Hz, 2 H), 7.49 - 7.54 (m, 3 H), 7.83 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 500.0; Anal. Calcd for C₂₅H₃₃N₅O₄S + 1.7 TFA + 0.6 H₂O: C, 48.43; H, 5.14; N, 9.94. Found: C, 48.44; H, 5.04; N, 10.04.

15 Example 80

N-(4-{[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide

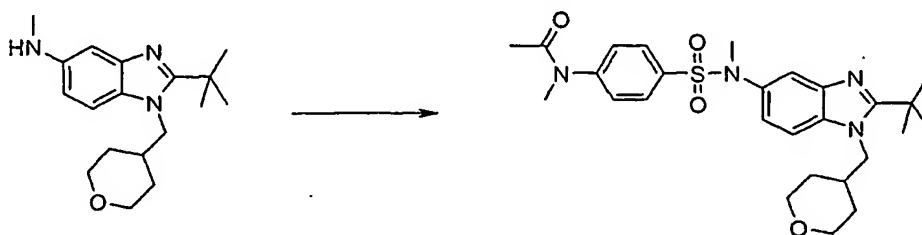


- 2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (200 mg, 0.663 mmol) and N-acetylsulfanilyl chloride (186 mg, 0.796 mmol) were stirred in 10 mL of DCM containing DMAP (16 mg, 0.133 mmol) at rt for 48h. The solution was washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title
 25 compound as the corresponding TFA salt. Yield: 353 mg (87%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.51 - 1.57 (m, 2 H), 1.56 - 1.65 (m, 2 H), 1.68 (s, 9 H), 2.14 (s, 3 H), 2.32 - 2.41 (m, 1 H), 3.25 (s, 3 H), 3.35 (td, J=11.47, 2.64 Hz, 2 H), 3.93 (d, J=2.93 Hz, 1 H), 3.96 (d, J=3.71 Hz, 1 H), 4.52 (d, J=7.62 Hz, 2 H), 7.32 (dd,

$J=8.98, 2.15$ Hz, 1 H), 7.45 (d, $J=8.98$ Hz, 2 H), 7.54 (d, $J=1.56$ Hz, 1 H), 7.71 (d, $J=8.98$ Hz, 2 H), 7.88 (d, $J=8.98$ Hz, 1 H); MS (ESI) (M+H)⁺: 499.0.

Example 81

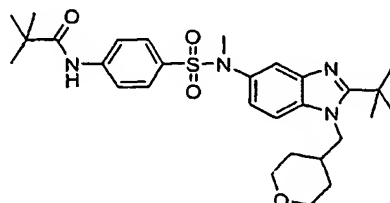
- 5 *N*-(4-[[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl)-*N*-methylacetamide



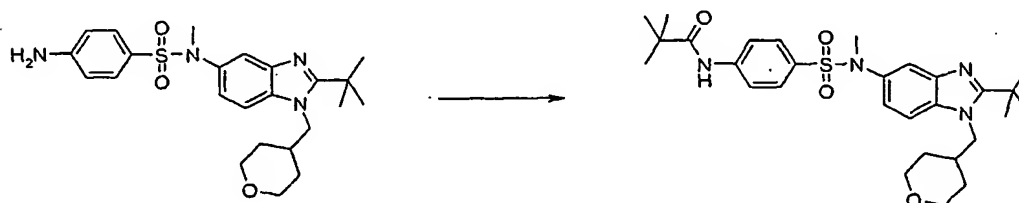
- 2-*tert*-Butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (37 mg, 0.123 mmol) and *N*-acetylsulfanilyl chloride (37 mg, 0.160 mmol) were stirred in 5 mL of DCM containing DMAP (catalytic) at rt overnight. The solution was washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was passed through a plug of silica gel using EtOAc as eluent and the solvent was evaporated. The product was dissolved in 5 mL of DMF at 0°C and NaH (60% dispersion in oil) (7 mg, 0.185 mmol) was added followed by iodomethane (0.012 mL, 0.185 mmol). The solution was stirred at rt for 2h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 28 mg (36%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.51 - 1.57 (m, 2 H), 1.57 - 1.64 (m, 2 H), 1.69 (s, 9 H), 2.00 (br.s, 3 H), 2.32 - 2.41 (m, 1 H), 3.29 - 3.30 (m, 6 H), 3.32 - 3.39 (m, 2 H), 3.93 (d, $J=2.93$ Hz, 1 H), 3.96 (d, $J=3.51$ Hz, 1 H), 4.53 (d, $J=7.42$ Hz, 2 H), 7.34 (dd, $J=8.98, 1.95$ Hz, 1 H), 7.48 (d, $J=8.79$ Hz, 2 H), 7.59 - 7.65 (m, 3 H), 7.90 (d, $J=8.98$ Hz, 1 H); MS (ESI) (M+H)⁺: 513.0; Anal. Calcd for C₂₇H₃₆N₄O₄S + 2.3 TFA + 0.2 H₂O: C, 48.75; H, 5.01; N, 7.20. Found: C, 48.69; H, 4.97; N, 7.39.

Example 82

N-(4-[[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl)-2,2-dimethylpropanamide

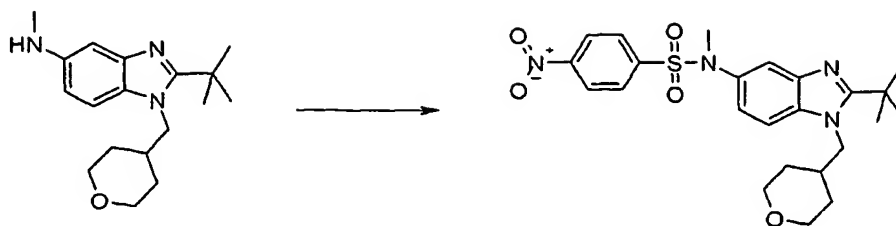


- 5 **Step A.** *N*-(4-[[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl)-2,2-dimethylpropanamide



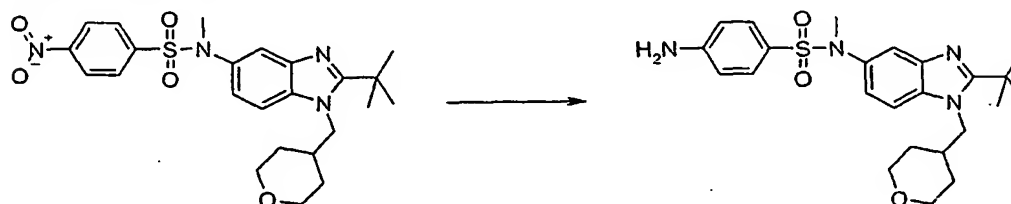
- 4-Amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (see following Steps B and C for preparation) (375 mg, 0.821 mmol) and trimethylacetyl chloride (0.120 mL, 0.985 mmol) were stirred in 20 mL of DCM containing a catalytic amount of DMAP at rt for 3h. The solution was washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was purified by reversed-phase HPLC using 10-75%
 15 CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 445 mg (83%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.29 (s, 9 H), 1.50 - 1.56 (m, 2 H), 1.57 - 1.65 (m, 2 H), 1.67 (s, 9 H), 2.32 - 2.40 (m, 1 H), 3.26 (s, 3 H), 3.35 (td, J=11.47, 2.64 Hz, 2 H), 3.93 (d, J=2.93 Hz, 1 H), 3.96 (d, J=3.32 Hz, 1 H), 4.51 (d, J=7.42 Hz, 2 H), 7.30 (dd, J=9.08, 2.05 Hz, 1 H), 7.45 (d, J=8.98 Hz, 2 H), 7.51 (d, J=1.95 Hz, 1 H), 7.75 (d, J=2.34 Hz, 1 H), 7.77 (d, J=2.34 Hz, 1 H), 7.86
 20 (d, J=8.98 Hz, 1 H), 9.39 (s, 1 H); MS (ESI) (M+H)⁺: 541.0.

Step B. *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-nitrobenzenesulfonamide



2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (280 mg, 0.929 mmol) and 4-nitrobenzenesulfonyl chloride (247 mg, 1.11 mmol) were stirred in 10 mL of DCM containing a catalytic amount of DMAP at rt overnight. The solution was washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes : EtOAc as eluent. Yield: 404 mg (89%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.51 - 1.57 (m, 13 H), 2.24 - 2.34 (m, 1 H), 3.27 (s, 3 H), 3.30 - 3.38 (m, 2 H), 3.99 (t, *J*=2.93 Hz, 1 H), 4.02 (t, *J*=3.03 Hz, 1 H), 4.20 (d, *J*=7.42 Hz, 2 H), 7.19 - 7.23 (m, 2 H), 7.29 - 7.33 (m, 1 H), 7.77 (d, *J*=8.98 Hz, 2 H), 8.30 (d, *J*=8.79 Hz, 2 H).

Step C. 4-Amino-N-[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylbenzenesulfonamide



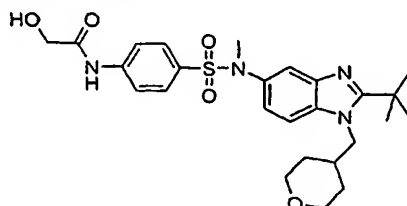
15

N-[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-*N*-methyl-4-nitrobenzenesulfonamide (400 mg, 0.822 mmol) was dissolved in 30 mL of 1:1 / EtOAc:EtOH containing a catalytic amount of 10% Pd/C. The solution was shaken under H₂ atmosphere (40 psi) using a Parr hydrogenation apparatus overnight at rt. The solution was filtered through celite and the solvent was evaporated. Yield: 375 mg (99%); MS (ESI) (*M*+H)⁺: 457.32.

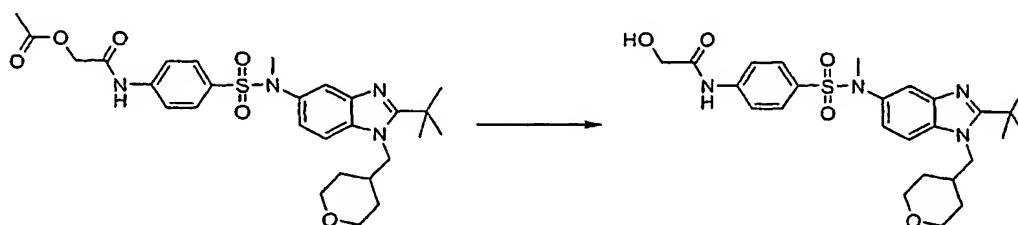
20

Example 83

N-(4-[[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-hydroxyacetamide



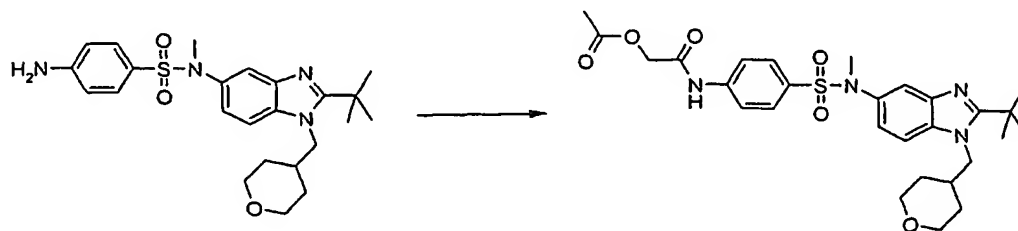
- 5 Step A. *N*-(4-[[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-hydroxyacetamide



- 2-[[4-[[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl]amino]-2-oxoethyl acetate (see following Step B
 10 for preparation) (45 mg, 0.0808 mmol) was dissolved in 3 mL of MeOH at 0°C. 25% NaOMe/MeOH (pH adjusted to 9.0) was added and solution was stirred at 0°C for 2h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous 5% KHSO₄ solution. The aqueous phase was basified with saturated aqueous NaHCO₃ solution and extracted with EtOAc (2X). The organic phase was washed
 15 with brine and dried over anhydrous MgSO₄. The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 35 mg (69%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.51 - 1.57 (m, 2 H), 1.57 - 1.65 (m, 2 H), 1.68 (s, 9 H), 2.32 - 2.41 (m, 1 H), 3.26 (s, 3 H), 3.35 (dt, J=11.47, 2.64 Hz, 2 H), 3.93 (d, J=2.93 Hz, 1
 20 H), 3.96 (d, J=3.71 Hz, 1 H), 4.13 (s, 2 H), 4.53 (d, J=7.62 Hz, 2 H), 7.33 (dd, J=9.08, 2.05 Hz, 1 H), 7.48 (d, J=8.98 Hz, 2 H), 7.54 (d, J=1.56 Hz, 1 H), 7.81 (d, J=8.98 Hz, 2 H), 7.89 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 515.0; Anal. Calcd for C₂₆H₃₄N₄O₅S + 2.2 TFA + 1.6 H₂O: C, 42.84; H, 4.48; N, 6.25. Found: C, 42.77; H, 4.28; N, 6.65.

25

Step B. 2-[(4-[[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl)amino]-2-oxoethyl acetate

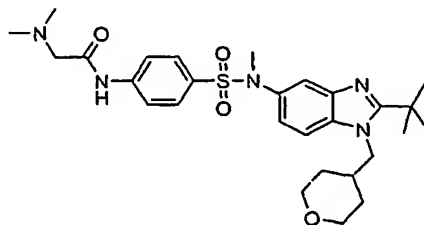


- 5 4-Amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (45 mg, 0.0986 mmol) and acetoxyacetyl chloride (0.013 mL, 0.118 mmol) were stirred in 2 mL of DCM containing a catalytic amount of DMAP at rt for 3h. The solution was washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by
- 10 silica gel flash chromatography using EtOAc as eluent. Yield: 45 mg (82%); ¹H NMR (400 MHz, CHLOROFORM-*D*): δ 1.50 - 1.55 (m, 13 H), 2.23 (s, 3 H), 2.25 - 2.33 (m, 1 H), 3.18 (s, 3 H), 3.29 - 3.37 (m, 2 H), 3.97 (t, *J*=2.83 Hz, 1 H), 4.00 (t, *J*=2.64 Hz, 1 H), 4.18 (d, *J*=7.23 Hz, 2 H) 4.67 - 4.71 (m, 2 H), 7.18 - 7.24 (m, 2 H), 7.24 - 7.29 (m, 1 H), 7.51 (d, *J*=8.79 Hz, 2 H), 7.62 (d, *J*=8.79 Hz, 2 H), 8.31 (s, 1 H).

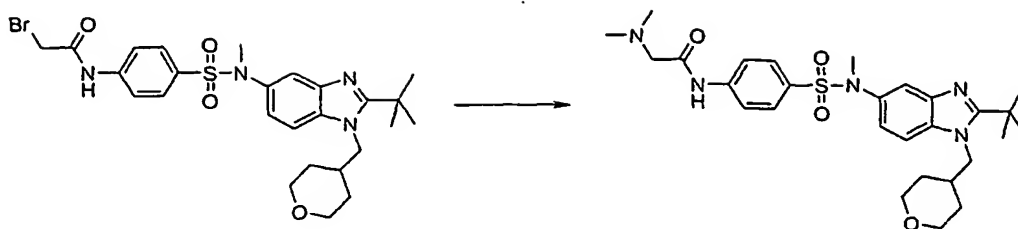
15

Example 84

*N*¹-(4-[[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl)-*N*²,*N*²-dimethylglycinamide

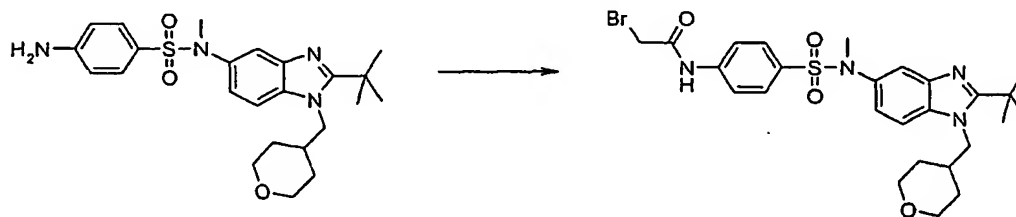


- 20 **Step A. *N*¹-(4-[[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl)-*N*²,*N*²-dimethylglycinamide**



- 2-Bromo-*N*-(4-({[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]}(methyl)amino)sulfonyl}phenyl)acetamide (see following Step B for preparation)
- 5 (36 mg, 0.0625 mmol) and dimethylamine hydrochloride (25 mg, 0.311 mmol) were stirred in 2 mL of DMF containing DIPEA (0.054 mL, 0.311 mmol) at 125°C for 15 min using a Personal Chemistry microwaves instrument. The solvent was evaporated. The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 34 mg
- 10 (83%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.50 - 1.55 (m, 2 H), 1.56 - 1.64 (m, 2 H), 1.66 (s, 9 H), 2.31 - 2.40 (m, 1 H), 2.99 (s, 6 H), 3.26 (s, 3 H), 3.35 (dt, J=11.47, 2.64 Hz, 2 H), 3.93 (d, J=2.93 Hz, 1 H), 3.96 (d, J=3.71 Hz, 1 H), 4.18 (s, 2 H), 4.49 (d, J=7.62 Hz, 2 H), 7.26 (dd, J=8.98, 2.15 Hz, 1 H), 7.52 (d, J=8.98 Hz, 2 H), 7.55 (d, J=1.95 Hz, 1 H), 7.76 (d, J=8.98 Hz, 2 H), 7.81 (d, J=8.79 Hz, 1 H); MS
- 15 (ESI) (M+H)⁺: 542.3; Anal. Calcd for C₂₈H₃₉N₅O₄S + 2.3 TFA + 1.0 H₂O: C, 47.64; H, 5.31; N, 8.52. Found: C, 47.68; H, 5.27; N, 8.55.

Step B. 2-Bromo-*N*-(4-({[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]}(methyl)amino)sulfonyl}phenyl)acetamide

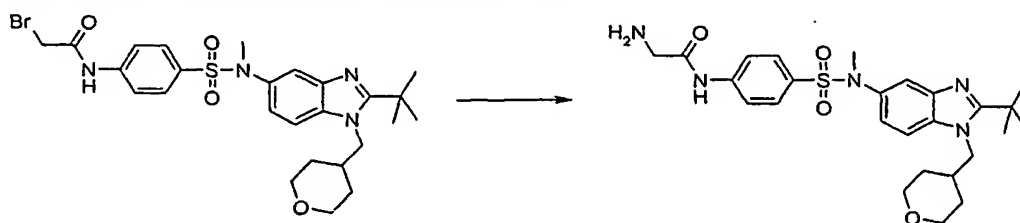


- 20 4-Amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (160 mg, 0.350 mmol) and bromoacetyl chloride (0.035 mL, 0.420 mmol) were stirred in 5 mL of DCM containing a catalytic amount of DMAP at rt for 3h. The solution was washed with saturated aqueous NaHCO₃

solution, brine and dried over anhydrous MgSO_4 . The crude product was purified by silica gel flash chromatography using EtOAc as eluent. Yield: 127 mg (63%); ^1H NMR (400 MHz, CHLOROFORM-D): δ 1.50 - 1.58 (m, 11 H), 1.59 - 1.67 (m, 2 H), 2.25 - 2.36 (m, 1 H), 3.21 (s, 3 H), 3.30 - 3.39 (m, 2 H), 3.99 (br.s, 1 H), 4.01 (br.s, 1 H), 4.05 (s, 1 H), 4.20 (d, $J=7.42$ Hz, 2 H) 4.23 (s, 1 H), 7.22 (s, 1 H), 7.24 - 7.30 (m, 2 H), 7.53 - 7.59 (m, 2 H), 7.63 - 7.70 (m, 2 H), 8.43 (d, $J=14.84$ Hz, 1 H).

Example 85

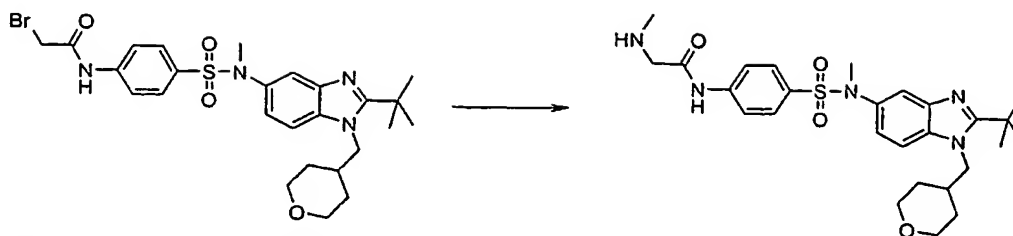
N^1 -(4-{[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino)sulfonyl}phenyl)glycinamide



Same procedure as in Step A in Example 84 using 2-bromo- N -(4-{[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino)sulfonyl}phenyl)acetamide (50 mg, 0.0866 mmol) and 28% (w/v) ammonia in water (0.5 mL) in 2 mL of DMF. The product was purified by reversed-phase HPLC using 10-60% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ and lyophilized affording the title compound as the corresponding TFA salt. Yield: 41 mg (75%); ^1H NMR (400 MHz, METHANOL-D_4): δ 1.50 - 1.56 (m, 2 H), 1.56 - 1.64 (m, 2 H), 1.67 (s, 9 H), 2.32 - 2.40 (m, 1 H), 3.26 (s, 3 H), 3.35 (dt, $J=11.47, 2.64$ Hz, 2 H), 3.89 (s, 2 H), 3.94 (d, $J=2.93$ Hz, 1 H), 3.96 (d, $J=3.32$ Hz, 1 H), 4.50 (d, $J=7.42$ Hz, 2 H), 7.27 (dd, $J=9.08, 2.05$ Hz, 1 H), 7.51 (d, $J=8.98$ Hz, 2 H), 7.56 (d, $J=1.76$ Hz, 1 H), 7.75 (d, $J=9.18$ Hz, 2 H), 7.83 (d, $J=8.79$ Hz, 1 H); MS (ESI) ($\text{M}+\text{H}$) $^+$: 514.0.

Example 86

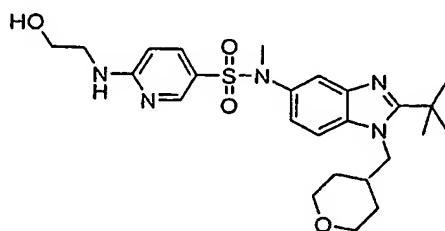
N^1 -(4-{[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino)sulfonyl}phenyl)- N^2 -methylglycinamide



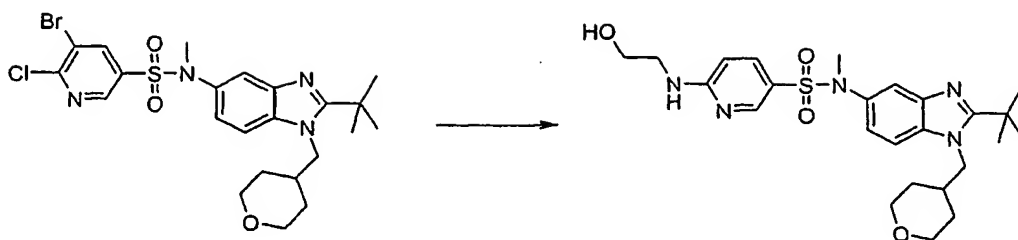
Same procedure as in Step A in Example 84 using 2-bromo-*N*-(4-({[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino)sulfonyl}phenyl)acetamide (30 mg, 0.0519 mmol), DIPEA (0.045 mL, 0.260 mmol) and methylamine hydrochloride (18 mg, 0.260 mmol) in 2 mL of DMF. The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 20 mg (60%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.49 - 1.57 (m, 2 H), 1.55 - 1.63 (m, 2 H), 1.66 (s, 9 H), 2.32 - 2.39 (m, 1 H), 2.78 (s, 3 H), 3.26 (s, 3 H), 3.35 (dt, J=11.42, 2.54 Hz, 2 H), 3.93 (d, J=2.93 Hz, 1 H), 3.96 (d, J=3.12 Hz, 1 H), 4.00 (s, 2 H), 4.48 (d, J=7.62 Hz, 2 H), 7.25 (dd, J=8.98, 1.95 Hz, 1 H), 7.52 (d, J=8.79 Hz, 2 H), 7.54 (d, J=1.95 Hz, 1 H), 7.75 (d, J=8.98 Hz, 2 H), 7.80 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 528.0.

15 Example 87

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-6-[(2-hydroxyethyl)amino]-*N*-methylpyridine-3-sulfonamide

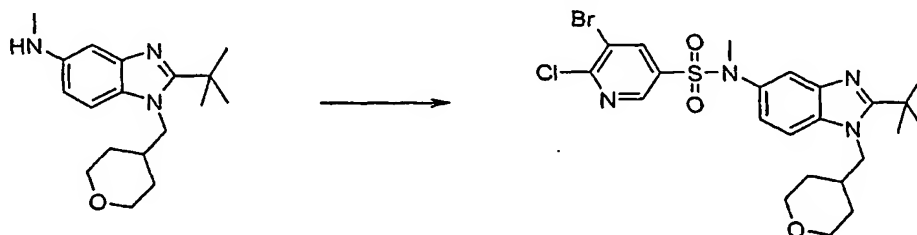


Step A. *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-6-[(2-hydroxyethyl)amino]-*N*-methylpyridine-3-sulfonamide



5-Bromo-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-6-chloro-*N*-methylpyridine-3-sulfonamide (see following Step B for preparation) (270 mg, 0.484 mmol) and ethanolamine (0.145 mL, 2.42 mmol) were stirred in 5 mL of DMF at 120°C for 3h. The solvent was concentrated. The product precipitated and was rinsed with ether. The product was dissolved in a 5:1 / EtOH:AcOH mixture (40 mL) containing a catalytic amount of 10% Pd/C and was shaken under H₂ atmosphere (50 psi) using a Parr hydrogenation apparatus at rt for 24h. The solution was filtered through celite and the solvent was evaporated. The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 240 mg (81%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.52 - 1.57 (m, 2 H), 1.58 - 1.65 (m, 2 H), 1.69 (s, 9 H), 2.33 - 2.41 (m, 1 H), 3.26 (s, 3 H), 3.36 (td, J=11.47, 2.64 Hz, 2 H), 3.48 (t, J=5.66 Hz, 2 H), 3.70 (t, J=5.57 Hz, 2 H), 3.93 (d, J=2.93 Hz, 1 H), 3.96 (d, J=3.71 Hz, 1 H), 4.53 (d, J=7.42 Hz, 2 H), 6.61 (d, J=8.98 Hz, 1 H), 7.41 (dd, J=9.08, 2.05 Hz, 1 H), 7.47 (dd, J=8.98, 1.95 Hz, 1 H), 7.61 (d, J=1.56 Hz, 1 H), 7.92 (d, J=9.18 Hz, 1 H), 7.99 (dd, J=2.44, 0.68 Hz, 1 H); MS (ESI) (M+H)⁺: 502.0; Anal. Calcd for C₂₅H₃₅N₅O₄S + 2.7 TFA: C, 45.11; H, 4.69; N, 8.65. Found: C, 45.18; H, 4.73; N, 8.43.

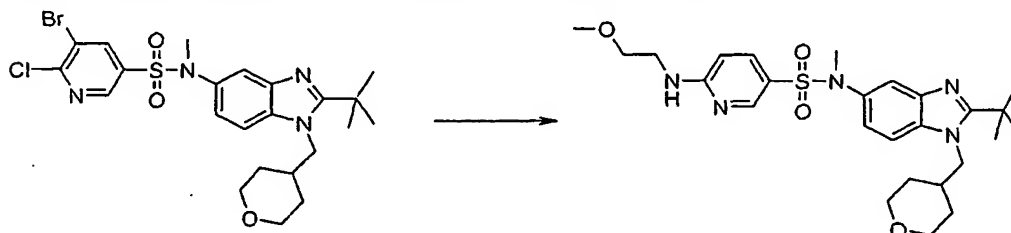
Step B. 5-Bromo-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-6-chloro-*N*-methylpyridine-3-sulfonamide



2-*tert*-Butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (180 mg, 0.597 mmol) and 3-bromo, 2-chloro-pyridine-5-sulphonyl chloride (225 mg, 0.776 mmol) were stirred in 5 mL of DCM containing a catalytic amount of DMAP at rt for 4h. The solution was washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes:EtOAc as eluent. Yield: 275 mg (83%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.51 - 1.60 (m, 13 H), 2.24 - 2.34 (m, 1 H), 3.30 (s, 3 H), 3.30 - 3.38 (m, 2 H), 3.99 (t, *J*=2.93 Hz, 1 H), 4.02 (t, *J*=2.93 Hz, 1 H), 4.20 (d, *J*=7.42 Hz, 2 H), 7.15 (dd, *J*=8.79, 1.76 Hz, 1 H), 7.29 - 7.33 (m, 2 H), 8.08 (d, *J*=2.15 Hz, 1 H), 8.39 (d, *J*=2.15 Hz, 1 H).

Example 88

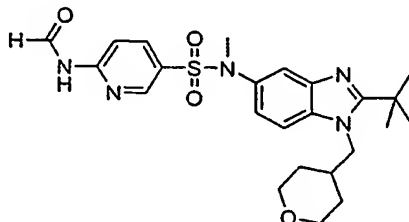
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-6-[(2-methoxyethyl)amino]-*N*-methylpyridine-3-sulfonamide



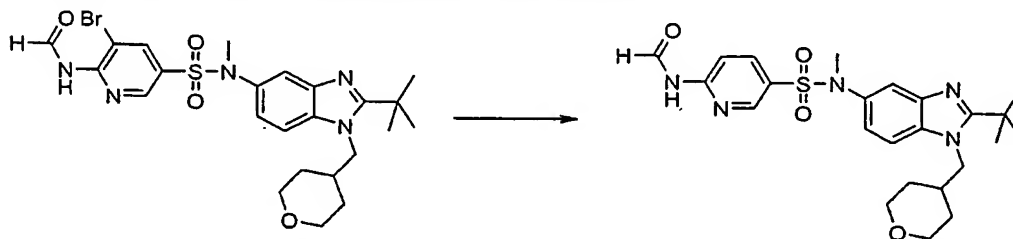
Following the same procedure as in Step A in Example 87 using 5-bromo-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-6-chloro-*N*-methylpyridine-3-sulfonamide (70 mg, 0.126 mmol) and 2-methoxyethylamine (0.055 mL, 0.630 mmol) in 2 mL of DMF. The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 36 mg (45%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.52 - 1.57 (m, 2 H), 1.57 - 1.66 (m, 2 H), 1.69 (s, 9 H), 2.33 - 2.42 (m, 1 H), 3.26 (s, 3 H), 3.32 - 3.39 (m, 5 H), 3.52 - 3.56 (m, 4 H), 3.93 (d, *J*=3.32 Hz, 1 H), 3.96 (d, *J*=3.91 Hz, 1 H), 4.53 (d, *J*=7.42 Hz, 2 H), 6.59 (d, *J*=9.18 Hz, 1 H), 7.41 (dd, *J*=9.08, 2.05 Hz, 1 H), 7.45 (dd, *J*=9.18, 1.95 Hz, 1 H), 7.61 (d, *J*=1.76 Hz, 1 H), 7.92 (d, *J*=8.98 Hz, 1 H), 8.00 (d, *J*=1.95 Hz, 1 H); MS (ESI) (*M*+*H*)⁺: 516.0.

Example 89

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-6-(formylamino)-*N*-methylpyridine-3-sulfonamide

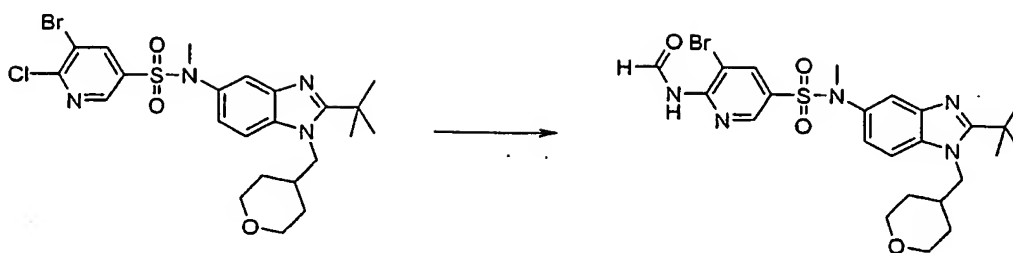


- 5 **Step A.** *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-6-(formylamino)-*N*-methylpyridine-3-sulfonamide



- N*-(3-Bromo-5-{[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methylamino)sulfonyl}pyridin-2-yl)acetamide (see following Step B for
10 preparation) (56 mg, 0.0992 mmol) was dissolved in 20 mL of EtOH containing a catalytic amount of 10% Pd/C. The solution was shaken under H₂ atmosphere (40 psi) using a Parr hydrogenation apparatus at rt overnight. The solution was filtered through celite and the solvent was evaporated. The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound
15 as the corresponding TFA salt. Yield: 36 mg (45%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.52 - 1.57 (m, 2 H), 1.57 - 1.66 (m, 2 H), 1.69 (s, 9 H), 2.33 - 2.42 (m, 1 H), 3.25 (s, 3 H), 3.35 (td, J=11.47, 2.83 Hz, 2 H), 3.93 (d, J=3.12 Hz, 1 H), 3.96 (d, J=3.71 Hz, 1 H), 4.54 (d, J=7.42 Hz, 2 H), 6.70 (d, J=9.18 Hz, 1 H), 7.40 (dd, J=8.98, 2.15 Hz, 1 H), 7.58 (dd, J=9.37, 2.54 Hz, 1 H), 7.60 (d, J=1.76 Hz, 1 H),
20 7.92 (d, J=8.98 Hz, 1 H), 8.05 (dd, J=2.54, 0.39 Hz, 1 H); MS (ESI) (M+H)⁺: 486.0.

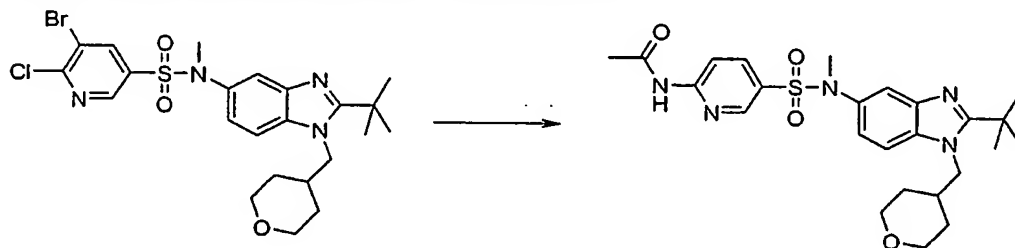
Step B. 5-Bromo-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-6-(formylamino)-*N*-methylpyridine-3-sulfonamide



5-Bromo-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-6-chloro-*N*-methylpyridine-3-sulfonamide (81 mg, 0.146 mmol) and 28% (w/v) ammonia in water (0.5 mL) were stirred in 3 mL of DMF at 120°C using a Personal Chemistry microwaves instrument for 30 min. The solvent was evaporated. The product was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using EtOAc as eluent. Yield: 56 mg (68%). MS (ESI) (M+H)⁺: 564.21.

Example 90

N-(5-{[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methylamino)sulfonyl}pyridin-2-yl)acetamide

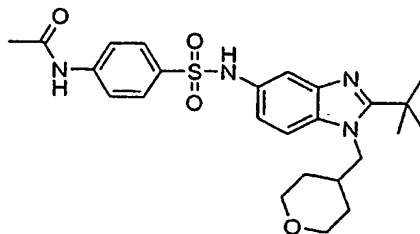


5-Bromo-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-6-chloro-*N*-methylpyridine-3-sulfonamide (275 mg, 0.495 mmol) and 28% (w/v) ammonia in water (1 mL) were dissolved in 4 mL of dioxane. The solution was stirred at 125°C using a Personal Chemistry microwaves instrument for 1 h. The solvent was evaporated. The product was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was dissolved in 25 mL of EtOH containing a catalytic amount of 10% Pd/C. The solution was shaken under H₂ atmosphere (40 psi) using a Parr hydrogenation

apparatus at rt overnight. The solution was filtered through celite and the solvent was evaporated. The residue was dissolved in 10 mL of 1:1 / DCE:pyridine and acetyl chloride (0.070 mL, 0.990 mmol) was added dropwise. The solution was stirred at rt for 3h. The solvent was evaporated. The product was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 170 mg (56%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.51 - 1.56 (m, 2 H), 1.57 - 1.64 (m, 2 H), 1.68 (s, 9 H), 2.18 (s, 3 H), 2.32 - 2.41 (m, 1 H), 3.29 - 3.31 (m, 3 H), 3.35 (td, J=11.52, 2.54 Hz, 2 H), 3.93 (d, J=3.12 Hz, 1 H), 3.96 (d, J=2.93 Hz, 1 H), 4.52 (d, J=7.42 Hz, 2 H), 7.35 (dd, J=9.08, 2.05 Hz, 1 H), 7.57 (d, J=1.95 Hz, 1 H), 7.80 (dd, J=8.88, 2.44 Hz, 1 H), 7.90 (d, J=8.98 Hz, 1 H), 8.24 (d, J=8.79 Hz, 1 H), 8.39 (d, J=2.15 Hz, 1 H); MS (ESI) (M+H)⁺:500.0; Anal. Calcd for C₂₅H₃₃N₅O₄S + 1.4 TFA + 0.3 H₂O: C, 50.24; H, 5.31; N, 10.54. Found: C, 50.25; H, 5.30; N, 10.44.

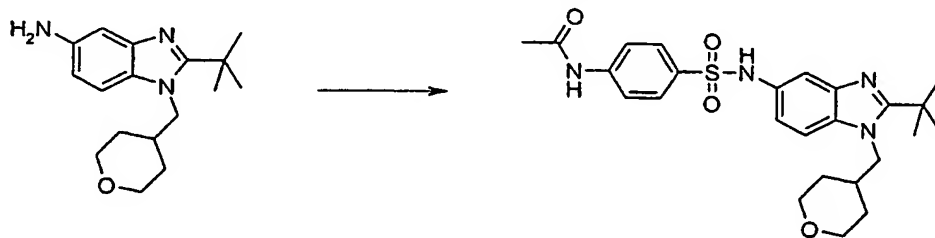
Example 91

N-[4-({[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]acetamide



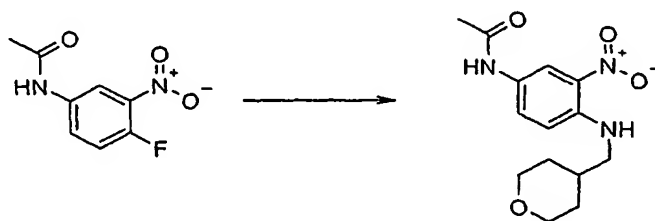
20

Step A. *N*-[4-({[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]acetamide



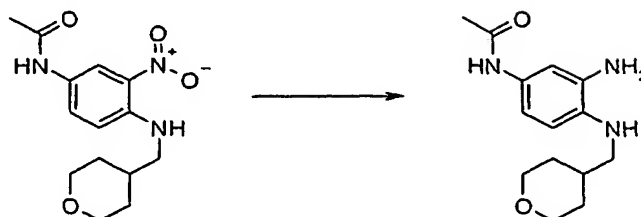
2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (for preparation see following Steps B, C, D, and E) (30 mg, 0.104 mmol) and 4-acetamidophenyl sulphonyl chloride (29 mg, 0.125 mmol) were stirred in 2 mL of DMF containing a catalytic amount of DMAP at rt for 4h. The solvent was
 5 evaporated and the product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 23 mg (37%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.45 - 1.51 (m, 2 H), 1.52 - 1.60 (m, 2 H), 1.63 (s, 9 H), 2.09 (s, 3 H), 2.26 - 2.36 (m, 1 H), 3.32 (dt, J= 11.42, 2.34 Hz, 2 H), 3.89 (d, J=2.93 Hz, 1 H), 3.92 (d, J=3.12 Hz, 1 H), 4.44 (d,
 10 J=7.62 Hz, 2 H), 7.24 (dd, J=8.98, 2.15 Hz, 1 H), 7.60 - 7.66 (m, 3 H), 7.62 - 7.73 (m, 2 H), 7.78 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 485.0; Anal. Calcd for C₂₅H₃₂N₄O₄S + 1.8 TFA + 0.5 H₂O: C, 49.15; H, 5.02; N, 8.02. Found: C, 49.09; H, 5.00; N, 8.21.

15 **Step B . *N*-{3-Nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide**



N-(4-Fluoro-3-nitrophenyl)acetamide (500 mg, 2.52 mmol) and 4-aminomethyl tetrahydropyran (350 mg, 3.02 mmol) were stirred in 20 mL of EtOH containing TEA
 20 (0.525 mL, 3.78 mmol) at 75°C overnight. The solvent was concentrated. The residue was dissolved in EtOAc and washed with aqueous 5% KHSO₄, saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using EtOAc as eluent. Yield: 611 mg (83%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.42 (ddd, J=25.19, 12.11, 4.49 Hz, 2 H), 1.74 (dd, J=12.89, 1.95 Hz, 2 H), 1.89 - 2.00 (m, 1H), 2.18 (s, 3 H), 3.22 (dd, J=6.44, 5.66 Hz, 2 H), 3.42 (dt, J=11.86, 2.05 Hz, 2 H), 4.02 (dd, J=10.94, 3.71 Hz, 2 H), 6.84 (d, J=9.37 Hz, 1 H), 7.20 (br.s, 1 H), 7.81 (dd, J=9.37, 2.54 Hz, 1 H), 8.09 (d, J=2.54 Hz, 1 H), 8.10 - 8.12 (m, 1 H).

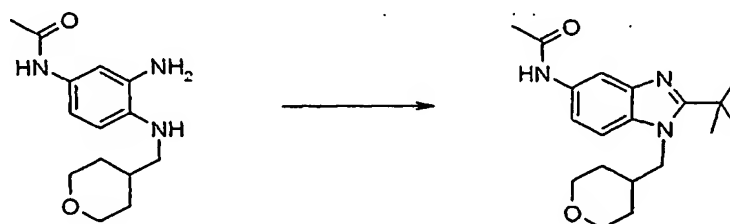
Step C . *N*-{3-Amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide



- 5 *N*-{3-Nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (605mg, 2.06 mmol) was dissolved in 50 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken under H₂ atmosphere (40 psi) using a Parr hydrogenation apparatus overnight at rt. The solution was filtered through celite and the solvent was evaporated. Yield: 315mg (58%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.40 (ddd, J=25.14, 12.06, 4.39 Hz, 2 H), 1.74 (dd, J=12.89, 1.95 Hz, 2 H), 1.82 – 1.91 (m, 1H), 2.13 (s, 3 H), 2.99 (d, J=6.64, 2 H), 3.42 (dt, J=11.86, 2.05 Hz, 2 H), 4.02 (dd, J=10.94, 3.71 Hz, 2 H), 6.84 (d, J=9.37 Hz, 1 H), 7.20 (br.s, 1 H), 7.81 (dd, J=9.37, 2.54 Hz, 1 H), 8.09 (d, J=2.54 Hz, 1 H), 8.10 – 8.12 (m, 1 H).

15

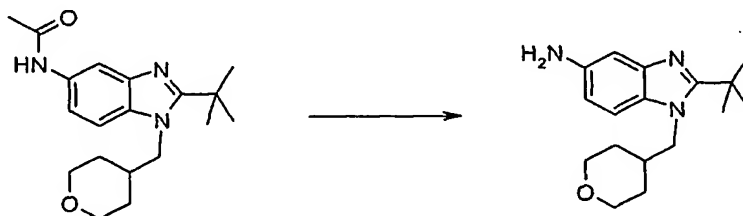
Step D . *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide



- 20 *N*-{3-Amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (315 mg, 1.20 mmol) and DMAP (30 mg, 0.240 mmol) were dissolved in 20 mL of DCM. Trimethylacetyl chloride (0.160 mL, 1.32 mmol) was added dropwise and the solution was stirred at rt for 2h. The solution was washed with aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The residue was dissolved in 3 mL of AcOH and was heated at 125°C for 1h using a Personal Chemistry microwave apparatus.

The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes : acetone as eluent. Yield: 135 mg (34%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.48 – 1.54 (m, 4 H), 1.56 (s, 9 H), 2.20 (s, 3 H), 2.24 – 2.35 (m, 1 H), 3.28 – 3.35 (m, 2 H), 3.96 (t, J= 2.83 Hz, 1 H), 3.99 (t, J= 3.03 Hz, 1 H), 4.19 (d, J=7.42 Hz, 2 H), 7.27 (d, J=8.59 Hz, 1 H), 7.34 (br.s, 1 H), 7.57 (dd, J=8.79, 1.95 Hz, 1 H), 7.67 (d, J=1.95 Hz, 1 H).

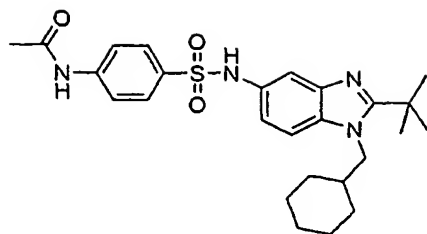
10 **Step E . 2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine**



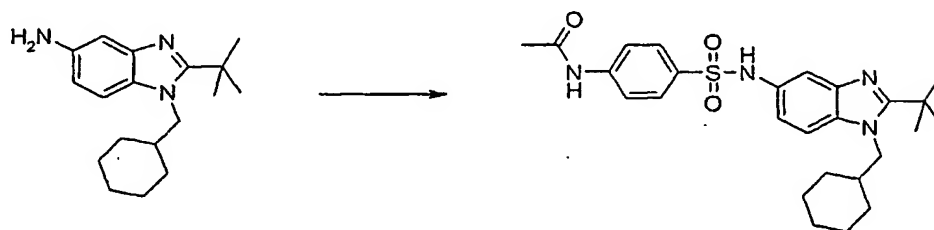
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide (135 mg, 0.409 mmol) was dissolved in 4 mL of 1:1 / EtOH:2M HCl. The solution was heated at 120°C for 30 min using a Personal Chemistry microwave apparatus. The solvent was evaporated. The residue was dissolved in EtOAc and washed with 2M NaOH solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. Yield: 117 mg (99%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.47 – 1.52 (m, 4 H), 1.54 (s, 9 H), 2.23 – 2.31 (m, 1 H), 3.28 – 3.36 (m, 2 H), 3.96 (t, J= 3.12 Hz, 1 H), 3.97 – 4.00 (m, 1 H), 4.13 (d, J=7.62 Hz, 2 H), 6.66 (dd, J=8.40, 2.15 Hz, 1 H), 7.06 (d, J=2.15 Hz, 1 H), 7.10 (d, J=8.40 Hz, 1 H).

Example 92

N-[4-({2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl}amino)sulfonyl]phenyl]acetamide

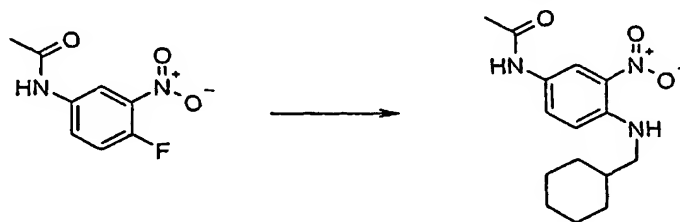


Step A. *N*-[4-({[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]acetamide



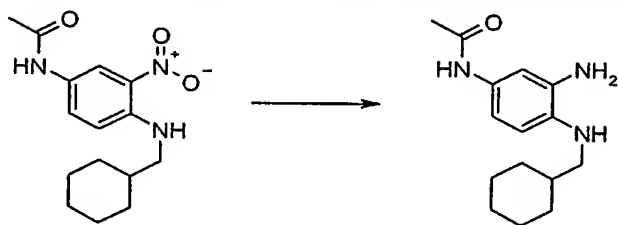
- 5 2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-amine (for preparation see following Steps, B, C, D, and E) (50 mg, 0.175 mmol) and 4-acetamidophenyl sulphonyl chloride (49 mg, 0.210 mmol) were stirred in 3 mL of DCM containing a catalytic amount of DMAP at rt for 4h. The solvent was evaporated and the product was purified by reversed-phase HPLC using 10-70% CH₃CN/H₂O and lyophilized
- 10 affording the title compound as the corresponding TFA salt. Yield: 80 mg (77%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.21 (m, 5 H), 1.59 (m, 1 H), 1.61 (m, 1 H), 1.63 (s, 9 H), 1.68 (m, 1 H), 1.75 (m, 2 H), 2.06 (m, 1 H), 2.10 (s, 3 H), 4.38 (d, J=7.62 Hz, 2 H), 7.25 (dd, J=9.08, 2.05 Hz, 1 H), 7.61 (d, J=1.56 Hz, 1 H), 7.66 (m, J=8.98 Hz, 2 H), 7.72 (m, 2 H), 7.76 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 483.3;
- 15 Anal. Calcd for C₂₆H₃₄N₄O₃S + 1.4 TFA + 0.5 H₂O: C, 53.11; H, 5.63; N, 8.60. Found: C, 53.03; H, 5.64; N, 8.72.

Step B. *N*-{4-[(Cyclohexylmethyl)amino]-3-nitrophenyl}acetamide



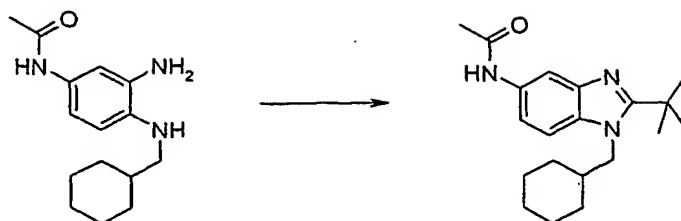
N-(4-Fluoro-3-nitrophenyl)acetamide (500 mg, 2.52 mmol) and cyclohexanemethylamine (0.400 mL, 3.02 mmol) were stirred in 15 mL of EtOH containing TEA (0.525 mL, 3.78 mmol) at 75°C overnight. The solvent was concentrated. The residue was dissolved in EtOAc and washed with aqueous 5% KHSO₄, saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. Yield: 735 mg (99%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.03 (m, 2 H), 1.25 (m, 3 H), 1.62 (m, 1 H), 1.69 (m, 1 H), 1.76 (m, 1 H), 1.79 (m, 1 H), 1.82 (m, 1 H), 1.86 (m, 1 H), 2.17 (s, 3 H), 3.14 (dd, J=6.25, 4.30 Hz, 2 H), 6.83 (d, J=9.37 Hz, 1 H), 7.20 (m, 1 H), 7.78 (dd, J=9.28, 2.64 Hz, 1 H), 8.07 (d, J=2.54 Hz, 1 H), 8.12 (m, 1 H).

Step C. *N*-(3-Amino-4-[(cyclohexylmethyl)amino]phenyl)acetamide



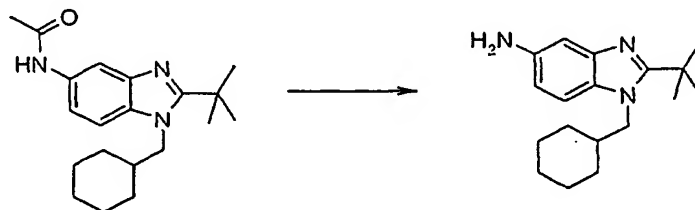
N-(4-[(Cyclohexylmethyl)amino]-3-nitrophenyl)acetamide (730 mg, 2.51 mmol) was dissolved in 40 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken under H₂ atmosphere (45 psi) using a Parr hydrogenation apparatus overnight at rt. The solution was filtered through celite and the solvent was evaporated. Yield: 629 mg (96%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.00 (m, 2 H), 1.25 (m, 4 H), 1.60 (m, 1 H), 1.69 (m, 1 H), 1.73 (m, 1 H), 1.76 (m, 1 H), 1.83 (m, 1 H), 1.86 (m, 1 H), 2.13 (s, 3 H), 2.91 (d, J=6.64, 2 H), 3.38 (m, 2 H), 6.56 (d, J=8.40 Hz, 1 H), 6.69 (dd, J=8.40, 2.15 Hz, 1 H), 7.01 (m, 1 H), 7.11 (d, J=2.34 Hz, 1 H).

Step D. *N*-(2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl)acetamide



- 5 *N*-{3-Amino-4-[(cyclohexylmethyl)amino]phenyl}acetamide (367 mg, 1.40 mmol) and DMAP (34 mg, 0.280 mmol) were dissolved in 10 mL of DCM. Trimethylacetyl chloride (0.190 mL, 1.54 mmol) was added dropwise and the solution was stirred at rt for 1h. The solvent was evaporated. The product was dissolved in 4 mL of AcOH and was stirred at 150°C for 45 min. The solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using 2:1 / hexanes : acetone as eluent. Yield: 268 mg (58%); ¹H
- 10 NMR (400 MHz, CHLOROFORM-D): δ 1.09 (m, 2 H), 1.17 (m, 3 H), 1.55 (s, 9 H), 1.62 (m, 1 H), 1.65 (m, 1 H), 1.69 (m, 1 H), 1.73 (m, 2 H), 2.03 (m, 1 H), 2.19 (s, 3 H), 4.11 (d, J=7.42, 2 H), 4.11 (d, J=7.42 Hz, 2 H), 7.27 (m, 1 H), 7.37 (m, 1 H), 7.55 (dd, J=8.69, 2.05 Hz, 1 H), 7.65(d, J=1.95 Hz, 1 H).

- 15 **Step E. 2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine**

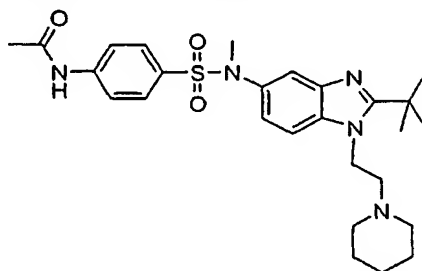


- 20 *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]acetamide (260 mg, 0.794 mmol) was dissolved in 4 mL of 1:1 / EtOH:2M HCl mixture. The solution was stirred at 170°C using a Personal Chemistry microwaves instrument for 30 min. The solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. Yield: 205 mg (90%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.08 (m, 2 H), 1.17 (m, 3 H), 1.53 (s, 9 H), 1.63 (m, 1 H),

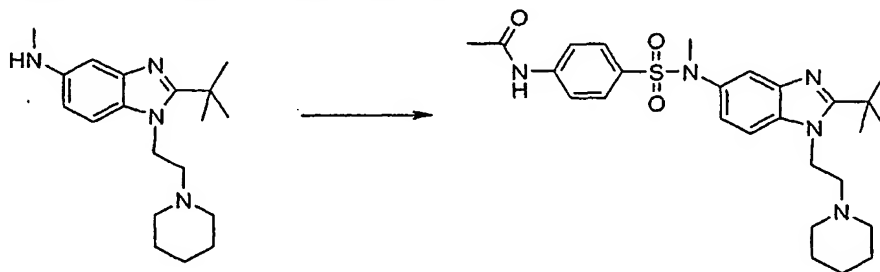
1.67 (m, 1 H), 1.72 (m, 1 H), 2.01 (m, 1 H), 3.58 (m, 1 H), 4.05 (d, J=7.42, 2 H), 6.64 (dd, J=8.59, 2.15 Hz, 2 H), 7.06 (d, J=1.95 Hz, 1 H), 7.11 (d, J=8.40 Hz, 1 H).

Example 93

5 *N*-(4-[[[2-*tert*-Butyl-1-(2-piperidin-1-ylethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl)acetamide



Step A. *N*-(4-[[[2-*tert*-Butyl-1-(2-piperidin-1-ylethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl)acetamide



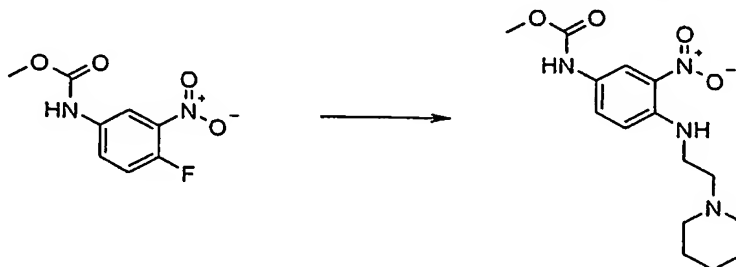
10

Same procedure used as in Step A of Example 92 using 2-*tert*-butyl-*N*-methyl-1-(2-piperidin-1-ylethyl)-1*H*-benzimidazol-5-amine (for preparation see following Steps B, C, D and E) (22 mg, 0.070 mmol) and 4-acetamidophenyl sulphonyl chloride (20 mg, 0.084 mmol) in 5 mL of DCM. The solvent was evaporated and the product was

15 purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 30 mg (68%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.64 (s, 9 H), 1.94 (m, 6 H), 2.15 (s, 3 H), 3.18 (m, 2 H), 3.25 (s, 3 H), 3.57 (m, 2 H), 4.98 (m, 2 H), 7.33 (dd, J=8.88, 2.05 Hz, 1 H), 7.44 (d, J=1.95 Hz, 1 H), 7.46 (d, J=8.98 Hz, 2 H), 7.72 (m, 3 H); MS (ESI) (M+H)⁺:

20 512.3; Anal. Calcd for C₂₇H₃₇N₃O₃S + 3.0 TFA + 0.8 H₂O: C, 45.66; H, 4.83; N, 8.07. Found: C, 45.67; H, 4.81; N, 8.02.

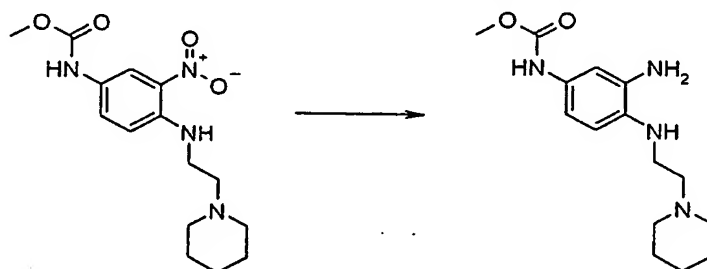
Step B. Methyl {3-nitro-4-[(2-piperidin-1-ylethyl)amino]phenyl}carbamate



Same procedure used as in Step B of Example 92 using methyl (4-fluoro-3-nitrophenyl)carbamate (75 mg, 0.350 mmol), TEA (0.075 mL, 0.525 mmol) and 1-aminoethylpiperidine (0.060 mL, 0.420 mmol). The crude product was purified by silica gel flash chromatography using EtOAc as eluent. Yield: 81 mg (72%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.46 (m, 2 H), 1.62 (m, 4 H), 2.45 (m, 4 H), 2.66 (t, J=6.35 Hz, 2 H), 3.36 (m, 2 H), 3.78 (s, 3 H), 6.46 (s, 1 H), 6.83 (d, J=9.37 Hz, 1 H), 7.64 (s, 1 H), 8.05 (d, J=2.73 Hz, 1 H), 8.41 (m, 1 H).

10

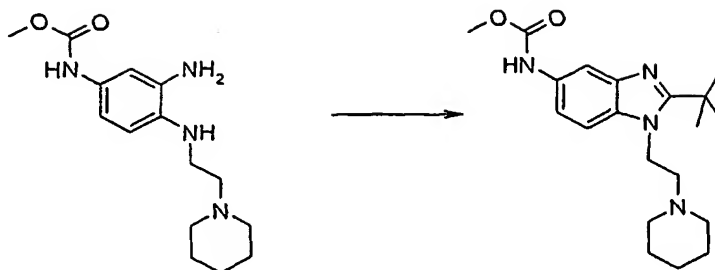
Step C. Methyl {3-amino-4-[(2-piperidin-1-ylethyl)amino]phenyl}carbamate



Same procedure used as in Step C of Example 92 using methyl {3-nitro-4-[(2-piperidin-1-ylethyl)amino]phenyl}carbamate (78 mg, 0.242 mmol) and a catalytic amount of 10% Pd/C in 15 mL of EtOAc. Yield: 56 mg (79%). MS (ESI) (M+H)⁺: 293.22.

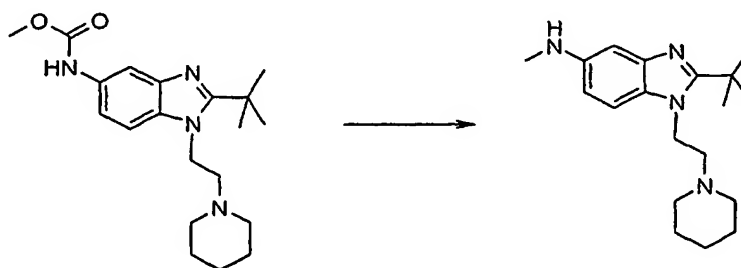
15

Step D. Methyl [2-*tert*-butyl-1-(2-piperidin-1-ylethyl)-1*H*-benzimidazol-5-yl]carbamate



- Methyl {3-amino-4-[(2-piperidin-1-ylethyl)amino]phenyl} carbamate (55 mg, 0.188 mmol) and trimethylacetyl chloride (0.025 mL, 0.207 mmol) were stirred in 5 mL of DCM containing a catalytic amount of DMAP at rt for 1h. The solution was washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. The residue was dissolved in 2 mL of AcOH and stirred at 150°C in a Personal Chemistry microwaves instrument for 40 min. The solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O. The fractions were concentrated. The residue was dissolved in EtOAc and washed with aqueous 2M NaOH solution, brine and dried over anhydrous MgSO₄. Yield: 27 mg (40%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.49 (m, 2 H), 1.55 (m, 9 H), 1.65 (m, 6 H), 2.55 (m, 2 H), 2.73 (m, 2 H), 3.78 (s, 3 H), 4.45 (m, 2 H), 4.45 (m, 2 H), 6.62 (m, 1 H), 7.26 (m, 1 H), 7.40 (m, 1 H), 7.61 (d, J=1.95 Hz, 1 H).

Step E. 2-*tert*-Butyl-*N*-methyl-1-(2-piperidin-1-ylethyl)-1*H*-benzimidazol-5-amine

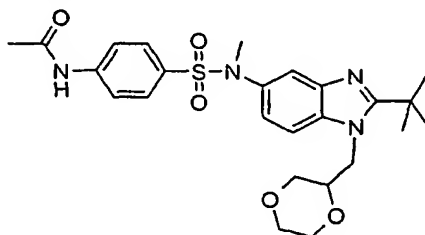


- Methyl [2-*tert*-butyl-1-(2-piperidin-1-ylethyl)-1*H*-benzimidazol-5-yl]carbamate (27 mg, 0.0753 mmol) was dissolved in 5 mL of THF at 0°C. 1M HCl/ether (0.115 mL, 0.113 mmol) was added and the solution was stirred at 0°C for 15 min. LiAlH₄ (15

mg, 0.377 mmol) was added and the solution was stirred at rt for 24h. The reaction was quenched at 0°C by the addition of MeOH (0.5 mL) and water (0.5 mL). Solid Na₂SO₄ (1g) was added and the solution was stirred at rt for 1h. The solution was filtered and rinsed with THF. The solvent was evaporated. Yield: 22 mg (93%); MS (ESI) (M+H)⁺: 315.03.

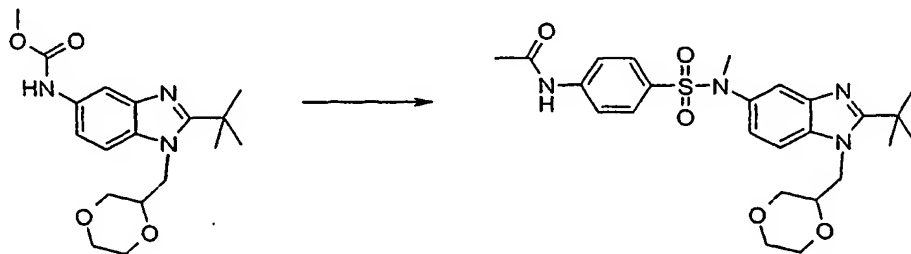
Example 94

N-(4-{[[2-*tert*-Butyl-1-(1,4-dioxan-2-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide



10

Step A. *N*-(4-{[[2-*tert*-Butyl-1-(1,4-dioxan-2-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide

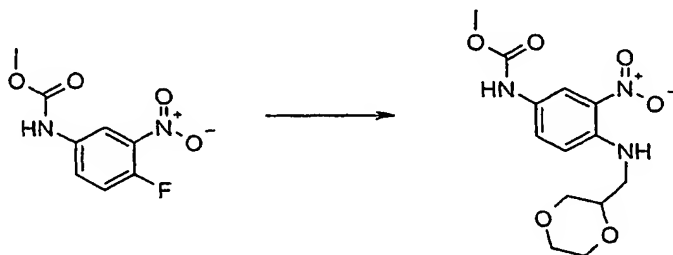


Methyl [2-*tert*-butyl-1-(1,4-dioxan-2-ylmethyl)-1*H*-benzimidazol-5-yl]carbamate (for preparation see following Steps B, C and D) (45 mg, 0.130 mmol) was dissolved in 5 mL of THF at 0°C. 1M HCl/ether (0.195 mL, 0.195 mmol) was added and the solution was stirred at 0°C for 15min. LiAlH₄ (25 mg, 0.650 mmol) was added and the solution was stirred at rt for 24h. The reaction was quenched at 0°C by the addition of MeOH (0.5 mL) and water (0.5 mL). Solid Na₂SO₄ (1g) was added and the solution was stirred at rt for 1h. The solution was filtered and rinsed with THF. The solvent was evaporated. The residue was dissolved in 3 mL of 1:1 / DCM:DMF solution containing a catalytic amount of DMAP. 4-Acetamidophenylsulfonyl chloride (35 mg, 0.156 mmol) was added and the solution was stirred at rt for 2h. The

solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O affording the title compound as its corresponding TFA salt. Yield: 26 mg (33%); ¹H NMR

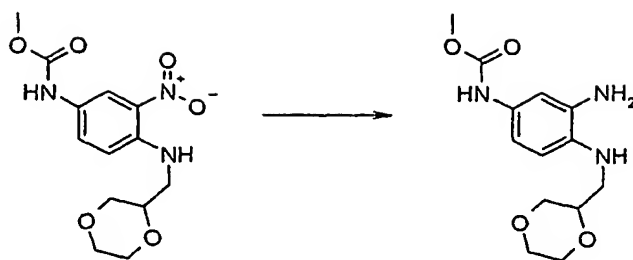
(400 MHz, METHANOL-D₄): δ 1.65 (s, 9 H), 2.13 (s, 3 H), 3.25 (s, 3 H), 3.50 (m, 2 H), 3.61 (dt, J=11.28, 2.44 Hz, 1 H), 3.67 (m, 1 H), 3.70 (m, 1 H), 4.00 (dd, J=11.52, 2.54 Hz, 1 H), 4.10 (m, 1 H), 4.63 (m, 2 H), 5.47 (s, 2 H), 7.28 (dd, J=9.08, 2.05 Hz, 1 H), 7.50 (d, J=1.76 Hz, 1 H), 7.70 (d, J=8.98 Hz, 2 H), 7.86 (d, J=8.79 Hz, 1 H); MS (ESI) (M+H)⁺: 501.0; Anal. Calcd for C₂₅H₃₂N₄O₅S + 1.5 TFA + 0.9 H₂O: C, 48.89; H, 5.17; N, 8.14. Found: C, 48.82; H, 5.12; N, 8.16.

Step B. Methyl {4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}carbamate



Same procedure used as in Step B of Example 92 using methyl (4-fluoro-3-nitrophenyl)carbamate (125 mg, 0.583 mmol), TEA (0.120 mL, 0.875 mmol) and C-[1,4]dioxane-2-yl-methylamine (82 mg, 0.700 mmol). The crude product was purified by silica gel flash chromatography using 50 to 75% EtOAc/hexanes as eluent. Yield: 94 mg (52%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 3.31 (m, 2 H), 3.46 (dd, J=11.42, 9.86 Hz, 1 H), 3.64 (dd, J=3.03, 0.88 Hz, 1 H), 3.66 (d, J=3.12 Hz, 1 H), 3.73 (m, 1 H), 3.76 (m, 4 H), 3.81 (dd, J=4.20, 2.64 Hz, 1 H), 3.84 (m, 1 H), 3.87 (m, 1 H), 6.46 (m, 1 H), 6.81 (d, J=9.18 Hz, 1 H), 7.63 (m, 1 H), 8.06 (d, J=2.54 Hz, 1 H).

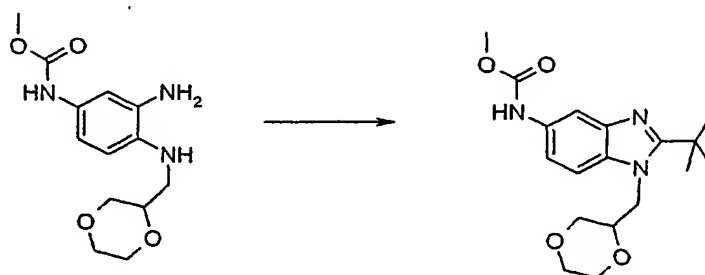
Step C. Methyl {3-amino-4-[(1,4-dioxan-2-ylmethyl)amino]phenyl}carbamate



Same procedure used as in Step C of Example 92 using methyl {4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl} carbamate (90 mg, 0.289 mmol) and a catalytic amount of 10% Pd/C in 15 mL of EtOAc. Yield: 81 mg (99%); MS (ESI) (M+H)⁺:

5 281.88.

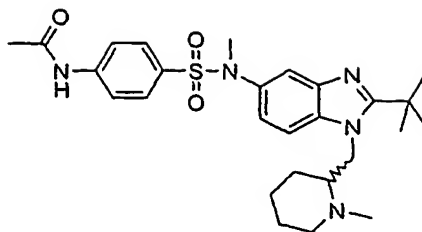
Step D. Methyl [2-*tert*-butyl-1-(1,4-dioxan-2-ylmethyl)-1*H*-benzimidazol-5-yl]carbamate



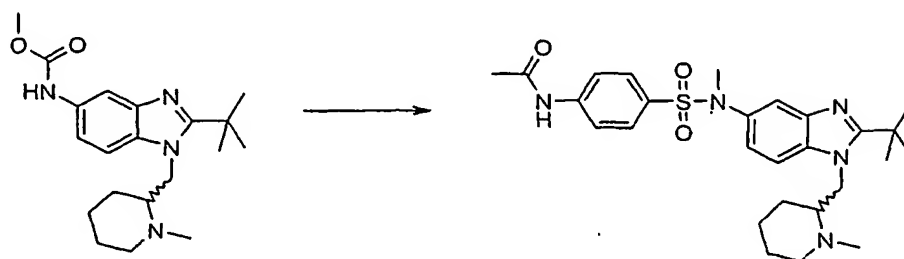
10 Same procedure as in Step D of Example 93 using methyl {3-amino-4-[(1,4-dioxan-2-ylmethyl)amino]phenyl} carbamate (81 mg, 0.288 mmol) and trimethylacetyl chloride (0.039 mL, 0.317 mmol). The crude product was purified by silica gel flash chromatography using EtOAc as eluent. Yield: 45 mg (45%).

15 **Example 95**

N-(4-[[[2-*tert*-Butyl-1-[(1-methylpiperidin-2-yl)methyl]-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl)acetamide



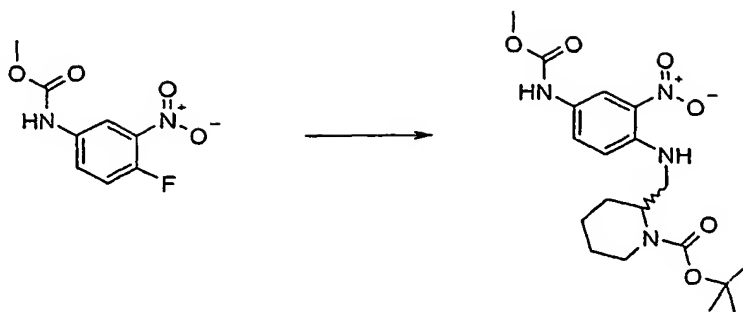
Step A. *N*-(4-{{[2-*tert*-Butyl-1-[(1-methylpiperidin-2-yl)methyl]-1*H*-benzimidazol-5-yl](methyl)amino)sulfonyl}phenyl)acetamide



- 5 Same procedure as in Step A of Example 94 using methyl {2-*tert*-butyl-1-[(1-methylpiperidin-2-yl)methyl]-1*H*-benzimidazol-5-yl}carbamate (for preparation see following Steps B, C, D, and E) (38 mg, 0.106 mmol), 1M HCl/ether (0.150 mL, 0.159 mmol), LiAlH₄ (20 mg, 0.530 mmol) in 5 mL of THF and 4-acetamidophenylsulfonyl chloride (30 mg, 0.127 mmol) in 5 mL of DCM. The
- 10 product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O affording the title compound as its corresponding TFA salt. Yield: 43 mg (65%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.39 (m, 2 H), 1.66 (s, 9 H), 1.84 (m, 2 H), 1.91 (m, 1 H), 2.15 (s, 3 H), 3.16 (s, 3 H), 3.25 (s, 3 H), 3.63 (m, 1 H), 4.02 (m, 1 H), 4.88 (m, 1 H), 5.19 (m, 1 H), 7.29 (dd, J=8.98, 2.15 Hz, 1 H), 7.46 (d, J=8.98 Hz, 2 H), 7.49 (d, J=1.76 Hz, 1 H), 7.71 (d, J=8.98 Hz, 2 H), 7.84 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 512.3; Anal. Calcd for C₂₇H₃₇N₅O₃S + 2.7 TFA + 1.0 H₂O: C, 46.46; H, 5.02; N, 8.36. Found: C, 46.46; H, 4.92; N, 8.59.
- 15

Step B. *tert*-Butyl 2-[(4-[(methoxycarbonyl)amino]-2-nitrophenyl)amino)methyl]piperidine-1-carboxylate

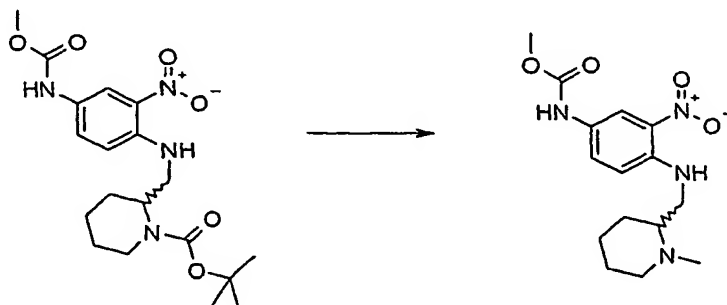
20



Same procedure used as in Step B of Example 92 using methyl (4-fluoro-3-nitrophenyl)carbamate (100 mg, 0.467 mmol), TEA (0.100 mL, 0.700 mmol) and 2-(aminomethyl)-1-N-Boc-piperidine (120 mg, 0.560 mmol). The crude product was
 5 purified by silica gel flash chromatography using 35 to 55% EtOAc/hexanes as eluent. Yield: 121 mg (63%); ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.46 (s, 9 H), 1.53 (m, 1 H), 1.65 (m, 1 H), 1.69 (m, 2 H), 1.72 (m, 2 H), 2.79 (m, 1 H), 3.33 (m, 1 H), 3.57 (m, 1 H), 3.78 (s, 3 H), 4.07 (m, 1 H), 6.47 (m, 1 H), 6.97 (d, J=9.57 Hz, 1 H), 7.66 (m, 1 H), 8.04 (m, 1 H), 8.07 (d, J=2.54 Hz, 1 H).

10

Step C. Methyl (4-((1-methylpiperidin-2-yl)methyl)amino)-3-nitrophenyl)carbamate

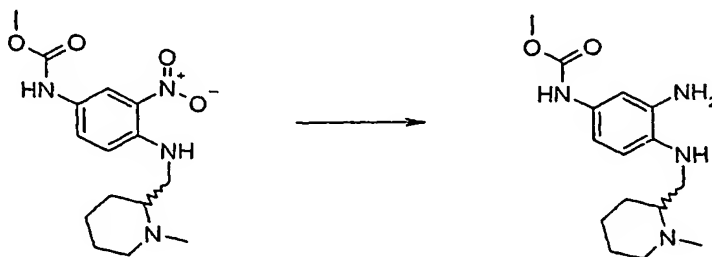


tert-Butyl 2-[(4-[(methoxycarbonyl)amino]-2-nitrophenyl)amino)methyl]piperidine-
 15 1-carboxylate (118 mg, 0.289 mmol) was stirred in 3 mL of 1M HCl/AcOH at rt for 1h. The solvent was evaporated. The residue was dissolved in 5 mL of MeOH and 37% HCHO/water (1 mL) was added, followed by NaBH(OAc)₃ (120 mg, 0.578 mmol). The solution was stirred at rt for 1h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous NaHCO₃
 20 solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. Yield:

87 mg (93%); ^1H NMR (400 MHz, CHCl_3 - d_3): δ 1.29 (m, 2 H), 1.61 (m, 5 H), 1.67 (m, 1 H), 1.78 (m, 1 H), 2.15 (m, 1 H), 2.22 (m, 1 H), 2.29 (s, 3 H), 2.93 (m, 1 H), 3.26 (m, 1 H), 3.43 (m, 1 H), 6.46 (m, 1 H), 6.79 (d, $J=9.37$ Hz, 1 H), 7.64 (m, 1 H), 8.05 (d, $J=2.54$ Hz, 1 H), 8.34 (m, 1 H).

5

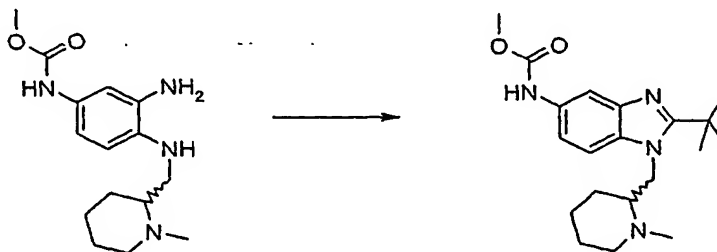
Step D. Methyl (3-amino-4-[[[(1-methylpiperidin-2-yl)methyl]amino]phenyl]carbamate



Same procedure used as in Step C of Example 92 using methyl (4-[[[(1-methylpiperidin-2-yl)methyl]amino]-3-nitrophenyl]carbamate (83 mg, 0.257 mmol) and a catalytic amount of 10% Pd/C in 20 mL of EtOAc. Yield: 75 mg (99%); MS (ESI) ($M+H$) $^+$: 293.26.

Step E. Methyl {2-*tert*-butyl-1-[[[(1-methylpiperidin-2-yl)methyl]-1*H*-benzimidazol-5-yl]}carbamate

15



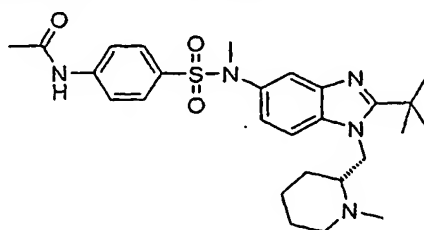
Same procedure as in Step D of Example 93 using methyl (3-amino-4-[[[(1-methylpiperidin-2-yl)methyl]amino]phenyl]carbamate (72 mg, 0.246 mmol) and trimethylacetyl chloride (0.033 mL, 0.271 mmol). The product was purified by reversed-phase HPLC using 10-50% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$. The fractions were concentrated. The residue was dissolved in EtOAc and washed with aqueous 2M NaOH solution, brine and dried over anhydrous MgSO_4 . Yield: 38 mg (43%); ^1H NMR (400 MHz,

CHLOROFORM-D): δ 1.07 (m, 2 H), 1.25 (m, 1 H), 1.56 (m, 9 H), 1.59 (m, 1 H), 1.63 (m, 1 H), 1.75 (m, 1 H), 2.20 (m, 1 H), 2.47 (s, 3 H), 2.68 (m, 1 H), 2.93 (d, $J=11.52$ Hz, 1 H), 3.78 (s, 3 H), 4.24 (dd, $J=14.25, 10.15$ Hz, 1 H), 4.66 (dd, $J=14.35, 5.17$ Hz, 1 H), 6.66 (m, 1 H), 7.31 (d, $J=8.59$ Hz, 1 H), 7.39 (m, 1 H), 7.60 (s, 1 H).

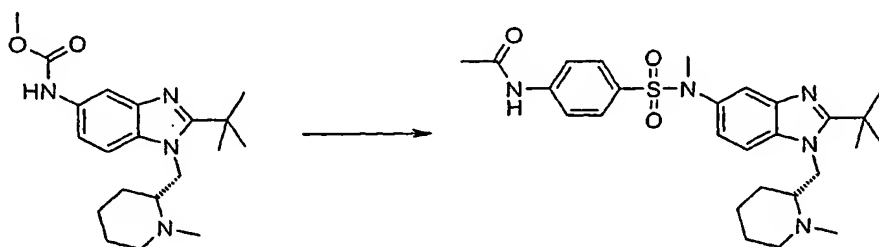
5

Example 96

N-(4-{{(2-*tert*-Butyl-1-{{(2*R*)-1-methylpiperidin-2-yl}methyl}-1*H*-benzimidazol-5-yl)(methyl)amino)sulfonyl}phenyl)acetamide



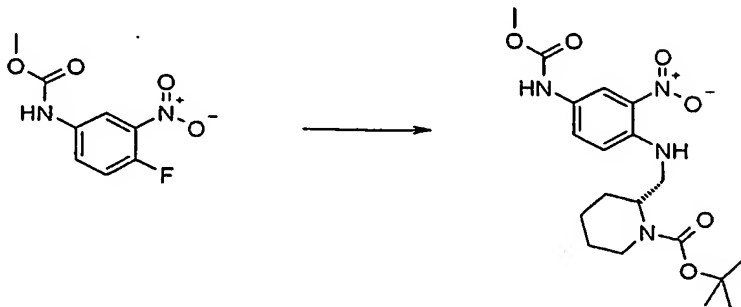
- 10 **Step A.** *N*-(4-{{(2-*tert*-Butyl-1-{{(2*R*)-1-methylpiperidin-2-yl}methyl}-1*H*-benzimidazol-5-yl)(methyl)amino)sulfonyl}phenyl)acetamide



- Same procedure as in Step A of Example 94 using methyl (2-*tert*-butyl-1-{{(2*R*)-1-methylpiperidin-2-yl}methyl}-1*H*-benzimidazol-5-yl)carbamate (for preparation see following Steps B, C, D, and E) (51 mg, 0.142 mmol), 1M HCl/ether (0.215 mL, 0.213 mmol), LiAlH₄ (27 mg, 0.710 mmol) in 5 mL of THF and 4-acetamidophenylsulfonyl chloride (40 mg, 0.170 mmol) in 5 mL of DCM. The product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O affording the title compound as its corresponding TFA salt. Yield: 59 mg (66%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.41 (m, 2 H), 1.65 (s, 9 H), 1.82 (m, 2 H), 1.89 (m, 2 H), 2.13 (s, 3 H), 3.15 (s, 3 H), 3.24 (s, 3 H), 3.62 (m, 1 H), 4.00 (m, 1 H), 4.86 (m, 1 H), 5.17 (m, 1 H), 7.29 (dd, $J=8.98, 1.95$ Hz, 1 H), 7.45 (d, $J=8.79$ Hz, 2 H), 7.49 (d, $J=1.95$ Hz, 1 H), 7.70 (d, $J=8.79$ Hz, 2 H), 7.83 (d, $J=8.98$ Hz, 1 H); MS (ESI)

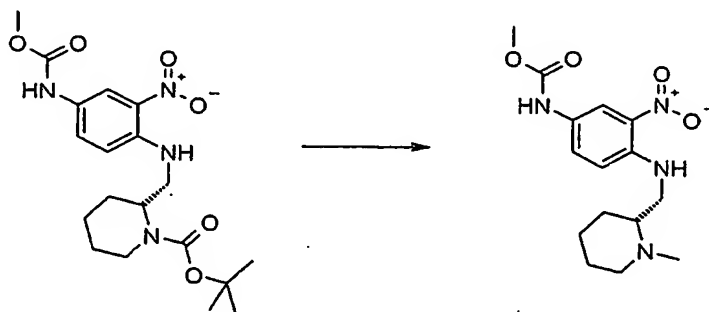
(M+H)⁺: 512.3; Anal. Calcd for C₂₇H₃₇N₅O₃S + 2.9 TFA + 1.2 H₂O: C, 45.60; H, 4.93; N, 8.11. Found: C, 45.64; H, 4.95; N, 8.05.

Step B. *tert*-Butyl (2*R*)-2-[(4-[(methoxycarbonyl)amino]-2-nitrophenyl)amino)methyl]piperidine-1-carboxylate



Same procedure used as in Step B of Example 92 using methyl (4-fluoro-3-nitrophenyl)carbamate (300 mg, 1.40 mmol), TEA (0.300 mL, 2.10 mmol) and 2-*R*-(aminomethyl)-1-*N*-Boc-piperidine (360 mg, 1.68 mmol). The crude product was purified by silica gel flash chromatography using 30 to 50% EtOAc/hexanes as eluent. Yield: 285 mg (50%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.46 (s, 9 H), 1.53 (m, 1 H), 1.65 (m, 1 H), 1.69 (m, 2 H), 1.72 (m, 2 H), 2.79 (m, 1 H), 3.33 (m, 1 H), 3.57 (m, 1 H), 3.78 (s, 3 H), 4.07 (m, 1 H), 6.47 (m, 1 H), 6.97 (d, J=9.57 Hz, 1 H), 7.66 (m, 1 H), 8.04 (m, 1 H), 8.07 (d, J=2.54 Hz, 1 H).

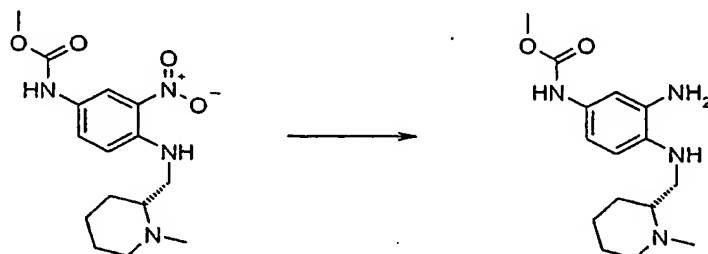
Step C. Methyl [4-(((2*R*)-1-methylpiperidin-2-yl)methyl)amino]-3-nitrophenyl]carbamate



Same procedure used as in Step C of Example 95 using *tert*-butyl (2*R*)-2-[(4-[(methoxycarbonyl)amino]-2-nitrophenyl)amino)methyl]piperidine-1-carboxylate

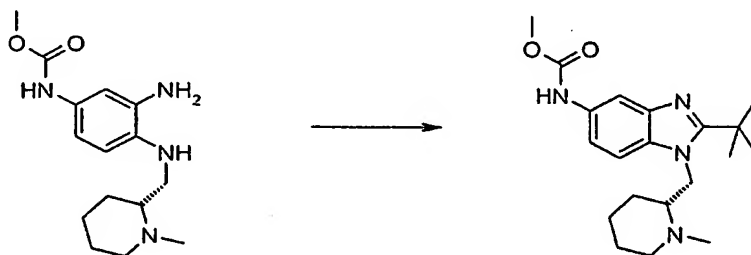
(280 mg, 0.686 mmol), 1M HCl/AcOH (3 mL), 37% HCHO/water (1 mL) and NaBH(OAc)₃ (290 mg, 1.37 mmol) in 5 mL of THF. Yield: 187 mg (85%); MS (ESI) (M+H)⁺: 323.27.

5 **Step D. Methyl [3-amino-4-({[(2R)-1-methylpiperidin-2-yl]methyl}amino)phenyl]carbamate**



Same procedure used as in Step C of Example 92 using methyl [4-({[(2R)-1-methylpiperidin-2-yl]methyl}amino)-3-nitrophenyl]carbamate (187 mg, 0.580 mmol) and a catalytic amount of 10% Pd/C in 25 mL of EtOAc. Yield: 164 mg (97%); MS (ESI) (M+H)⁺: 293.24.

15 **Step E. Methyl (2-*tert*-butyl-1-({[(2R)-1-methylpiperidin-2-yl]methyl}-1H-benzimidazol-5-yl)carbamate**

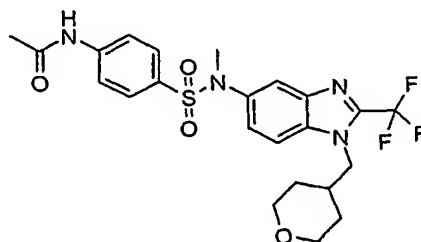


Same procedure as in Step D of Example 93 using methyl [3-amino-4-({[(2R)-1-methylpiperidin-2-yl]methyl}amino)phenyl]carbamate (160 mg, 0.547 mmol) and trimethylacetyl chloride (0.075 mL, 0.602 mmol). The product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O. The fractions were concentrated. The residue was dissolved in EtOAc and washed with aqueous 2M NaOH solution, brine and dried over anhydrous MgSO₄. Yield: 55 mg (28%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.08 (m, 2 H), 1.29 (m, 1 H), 1.57 (s, 9 H), 1.61 (m, 3 H),

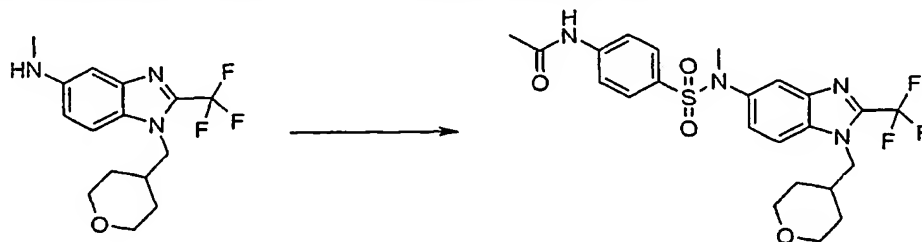
2.22 (m, 1 H), 2.49 (s, 3 H), 2.72 (m, 1 H), 2.96 (m, 1 H), 3.78 (s, 3 H), 4.26 (dd, $J=14.35, 4.98$ Hz, 1 H), 6.62 (s, 1 H), 7.32 (d, $J=8.59$ Hz, 1 H), 7.39 (m, 1 H), 7.61 (s, 1 H).

5 Example 97

N-[4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]acetamide



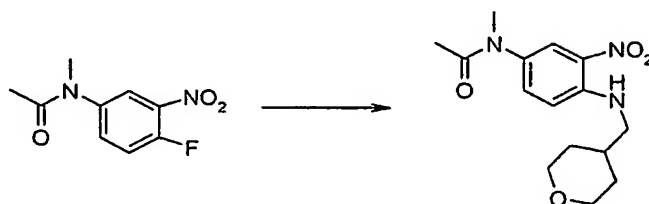
Step A. *N*-[4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]acetamide



N-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-amine hydrochloride (76.1 mg, 0.2 mmol) (for preparation, see the following steps B, C, D, and E), DMAP (97.7 mg, 0.8 mmol) and 4-(acetylamino)benzenesulfonyl chloride (93.5 mg, 0.4 mmol) in MeCN (5 mL) were stirred overnight at room temperature. The reaction mixture was quenched with H₂O (6 mL). Upon evaporation, the crude product was purified by reversed-phase HPLC using 20-70% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 49.1 mg (48%); ¹HNMR (400 MHz, CD₃OD): 1.39 - 1.56 (m, 4 H), 2.14 (s, 3 H), 2.19 - 2.32 (m, 1 H), 3.24 (s, 3 H), 3.31 - 3.39 (m, 2 H), 3.85 - 4.01 (m, 2 H), 4.32 (d, $J=7.42$ Hz, 2 H), 7.32 (dd, $J=8.88, 2.05$ Hz, 1 H), 7.40 (d, $J=1.95$ Hz, 1 H), 7.43 - 7.49 (m, 2 H), 7.67 - 7.75 (m, 3 H); MS (ESI) ($M+H$)⁺: 511.0; Anal. Calcd for

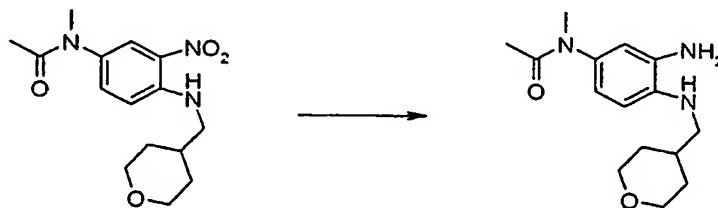
$C_{23}H_{25}F_3N_4O_4S + 0.4 \text{ TFA} + 0.2 \text{ H}_2\text{O}$ (559.75): C, 51.07, H, 4.65, N, 10.01; Found: C, 51.16; H, 4.74; N, 9.65.

5 **Step B . *N*-methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide**



4-Aminomethylpyran (2.50 g, 21.7 mmol) was added to a mixture of *N*-(4-fluoro-3-nitrophenyl)-*N*-methylacetamide (4.61 g, 21.27 mmol) and sodium carbonate (5.10 g, 47.7 mmol) in EtOH (120 mL) at room temperature. The reaction mixture was heated for 3 days at 60 °C. Upon evaporation of ethanol, the residue was dissolved in EtOAc (400 mL), washed with H₂O (3x50 mL), saturated NaCl (3x50 mL), and dried over Na₂SO₄. After filtration and concentration, 6.62 g (100%) of the title compound was obtained as an orange-red solid. ¹H NMR (400 MHz, CDCl₃): δ 1.38 - 1.52 (m, 2 H), 1.72 - 1.81 (m, 2 H), 1.90 (s, 3 H), 1.93 - 2.02 (m, 1 H), 3.23 (s, 3 H), 3.23 - 3.27 (m, 2 H), 3.36 - 3.49 (m, 2 H), 4.01 - 4.07 (m, 2 H), 6.91 (d, *J*=9.18 Hz, 1 H), 7.29 (dd, *J*=9.08, 2.64 Hz, 1 H), 8.05 (d, *J*=2.34 Hz, 1 H), 8.22 (t, *J*=5.37 Hz, 1 H); MS (ESI) (M+H)⁺: 309.12.

20 **Step C . *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide**



N-methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (5.39 g, 16.7 mmol) was hydrogenated in ethyl acetate (200 mL) catalyzed by 10%

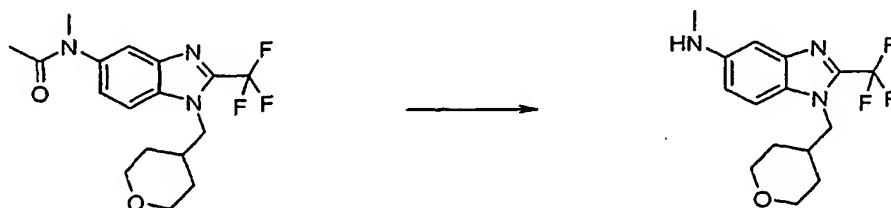
Pd/C (0.2 g) at 30-40 psi H₂ in Parr shaker for 18 h at room temperature. After filtration through celite and concentration, 6.0 g (100%) of a purple solid was obtained as HCl salt, which was used in the next step without further purification. ¹H NMR (400 MHz, CD₃OD): δ 1.32 - 1.46 (m, 2 H), 1.78 - 1.84 (m, 2 H), 1.85 (s, 3 H), 1.91 - 2.06 (m, 1 H), 3.16 (d, *J*=6.83 Hz, 2 H), 3.20 (s, 3 H), 3.39 - 3.51 (m, 2 H), 3.94 - 4.03 (m, 2 H), 7.01 (d, *J*=8.59 Hz, 1 H), 7.12 (d, *J*=2.15 Hz, 1 H), 7.17 (dd, *J*=8.49, 4.39 Hz, 1 H); MS (ESI) (M+H)⁺: 278.7.

Step D . *N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]acetamide



A solution of *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide hydrochloride (395.1 mg, 1.42 mmol) in trifluoroacetic acid (10 mL) was heated to reflux for 20 h. After evaporation of the solvent, the crude product was used directly for next step without further purification. MS (ESI) (M+H)⁺: 356.02.

Step E . *N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-amine

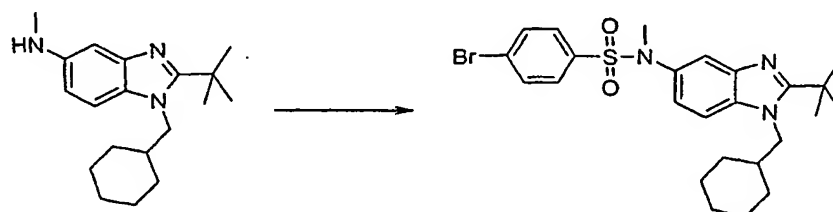


The crude *N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]acetamide (~500 mg, 1.42 mmol) was dissolved in 10 mL of EtOH-2*N* HCl (3:2), and then heated at 120°C in a Personal Chemistry SmithSynthesizer microwave instrument for 4 h. After concentration and dried *in*

vacuo, 539 mg (100%) of a grey white solid was obtained as the title product, which was used directly for Step A. MS (ESI) (M+H)⁺: 314.20.

Example 98

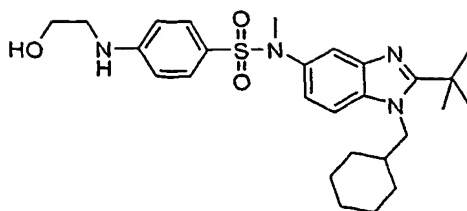
5 4-Bromo-*N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzenesulfonamide



N-1-(Cyclohexylmethyl)-2-(1,1-dimethylethyl)-*N*-methyl-1*H*-benzimidazol-5-amine hydrochloride (532.2 mg, 1.39 mmol) (for preparation, see Example 39), DMAP (679.3 mg, 5.56 mmol) and 4-bromobenzenesulfonyl chloride (426.7 mg, 1.67 mmol) in MeCN (50 mL) were stirred overnight at room temperature. The reaction mixture was quenched with saturated NaHCO₃ (10 mL), evaporated to small volume and extracted with EtOAc (3x50 mL). The combined organic phases were washed with
15 brine and dried over Na₂SO₄. After evaporation of the solvent, the product was purified by MPLC using Hexanes/EtOAc (1:1) on silica gel to give 529.6 mg (74%) of a white solid as the title product. A small amount of the title product was converted to the corresponding TFA salt. ¹H NMR (400 MHz, CD₃OD): δ 1.26 (m, 5 H), 1.64 (m, 2 H), 1.67 (s, 9 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 3.29 (s,
20 3 H), 4.45 (d, J=7.62 Hz, 2 H), 7.31 (m, 1 H), 7.45 (m, 2 H), 7.53 (d, J=1.56 Hz, 1 H), 7.72 (m, 2 H), 7.85 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 518.2; Anal. Calcd for C₂₅H₃₂BrN₃O₂S+1.00 TFA+1.40 H₂O (639.75): C, 50.69; H, 5.33; N, 6.57; Found: C, 50.75; H, 5.40; N, 6.47.

25 Example 99

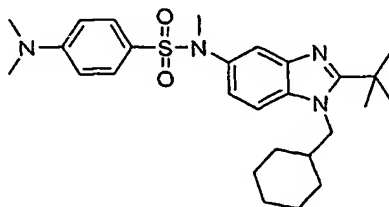
N-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-4-[(2-hydroxyethyl)amino]-*N*-methylbenzenesulfonamide



4-Bromo-*N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (21.0 mg, 0.0405 mmol) (for preparation, see Example 40) and ethanolamine (1.0 mL) were placed in a sealed tube. The mixture was heated at 220°C in a Personal Chemistry SmithSynthesizer microwave instrument for 1.5 h, and purified by reversed-phase HPLC using 15-60% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 20.8 mg (84%); ¹H NMR (400 MHz, CD₃OD): δ 1.24 (m, 5 H), 1.63 (m, 2 H), 1.66 (s, 9 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 3.20 (s, 3 H), 3.26 (t, J=5.76 Hz, 2 H), 3.70 (t, J=5.86 Hz, 2 H), 4.44 (d, J=7.62 Hz, 2 H), 6.61 (m, 2 H), 7.23 (m, 2 H), 7.32 (dd, J=8.98, 2.15 Hz, 1 H), 7.51 (d, J=1.95 Hz, 1 H), 7.81 (d, J=9.18 Hz, 1 H); MS (ESI) (M+H)⁺: 499.2; Anal. Calcd for C₂₇H₃₈N₄O₃S+1.60 TFA+2.30 H₂O+0.3 MeCN (734.88): C, 50.34; H, 6.19; N, 8.20; Found: C, 50.40; H, 6.17; N, 8.18.

Example 100

N-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-4-(dimethylamino)-*N*-methylbenzenesulfonamide

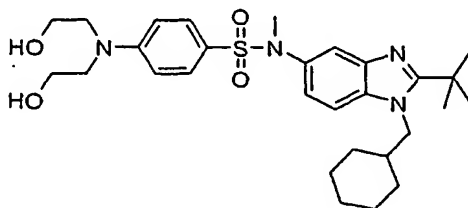


Following the procedure for Example 99, using 4-Bromo-*N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (31.6 mg, 0.0609 mmol) (for preparation, see Example 98) and ethanolamine (0.5 mL) in DMF (1.0 mL), the crude product was purified by reversed-phase HPLC using 15-60% CH₃CN/H₂O and then lyophilized affording 20.4 mg (56%) of the title compound and 12.8 mg (34%) of the title compound in Example 41 as the corresponding TFA salt.

¹H NMR (400 MHz, CD₃OD): δ 1.25 (m, 5 H), 1.63 (m, 2 H), 1.67 (s, 9 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 3.03 (s, 6 H), 3.21 (s, 3 H), 4.44 (d, J=7.62 Hz, 2 H), 6.70 (m, 2 H), 7.31 (m, 3 H), 7.52 (d, J=1.95 Hz, 1 H), 7.82 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 483.3; Anal. Calcd for C₂₇H₃₈N₄O₂S+1.50 TFA+1.10 H₂O (673.55): C, 53.50; H, 6.24; N, 8.32, Found: C, 53.42; H, 6.20; N, 8.42.

Example 101

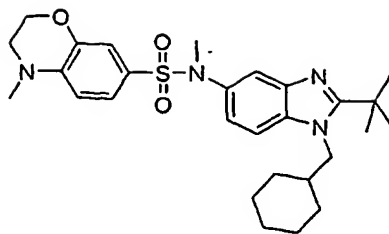
4-[bis(2-hydroxyethyl)amino]-N-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-N-methylbenzenesulfonamide



Following the procedure for Example 99, using 4-Bromo-N-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-N-methyl-benzenesulfonamide (31.2 mg, 0.0602 mmol) (for preparation, see Example 40) and 2,2'-iminodiethanol (1.0 mL), the crude product was purified by reversed-phase HPLC using 15-60% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 25.3 mg (64%); ¹H NMR (400 MHz, CD₃OD): 1.25 (m, 5 H), 1.64 (m, 2 H), 1.67 (s, 9 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 2.10 (m, 1 H), 3.22 (s, 3 H), 3.60 (t, J=5.86 Hz, 4 H), 3.72 (t, J=5.86 Hz, 4 H), 4.45 (d, J=7.62 Hz, 2 H), 6.77 (m, 2 H), 7.30 (m, 2 H), 7.33 (m, 1 H), 7.54 (d, J=1.95 Hz, 1 H), 7.83 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 543.2; Anal. Calcd for C₂₉H₄₂N₄O₄S+1.60 TFA+0.4 H₂O (732.39): C, 52.81; H, 6.11; N, 7.65, Found: C, 52.85; H, 6.06; N, 7.69.

Example 102

N-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-N,4-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine-7-sulfonamide

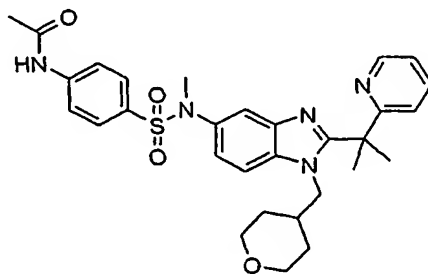


Following the procedure as in Example 98, using *N*-1-(Cyclohexylmethyl)-2-(1,1-dimethylethyl)-*N*-methyl-1*H*-benzimidazol-5-amine hydrochloride (33.0 mg, 0.0886 mmol) (for preparation, see the step F in Example 40), DMAP (43.3 mg, 0.354 mmol) and 4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-7-sulfonyl chloride (28.5 mg, 0.115 mmol) in MeCN (5 mL), the crude product was purified by reversed-phase HPLC using 20-70% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 43.3 mg (78%); ¹H NMR (400 MHz, CD₃OD): δ 1.25 (m, 5 H), 1.64 (m, 2 H), 1.67 (s, 9 H), 1.70 (m, 1 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 2.72 (s, 3 H), 3.24 (s, 3 H), 3.28 (m, 2 H), 4.31 (m, 2 H), 4.46 (d, J=7.42 Hz, 2 H), 6.66 (s, 1 H), 6.77 (m, 2 H), 7.32 (m, 1 H), 7.57 (d, J=1.37 Hz, 1 H), 7.85 (d, J=7.62 Hz, 1 H); MS (ESI) (M+H)⁺: 511.2; Anal. Calcd for C₂₈H₃₈N₄O₃S+1.40 TFA+0.40 H₂O (677.54): C, 54.60; H, 5.98; N, 8.27, Found: C, 54.48; H, 5.89; N, 8.52.

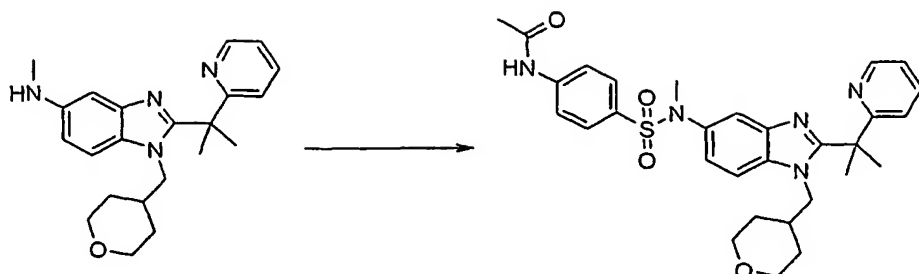
15

Example 103

N-[4-({methyl[2-(1-methyl-1-pyridin-2-ylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]acetamide



20 Step A. *N*-[4-({methyl[2-(1-methyl-1-pyridin-2-ylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]acetamide



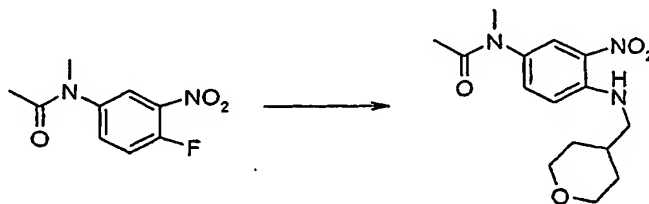
N-methyl-2-(1-methyl-1-pyridin-2-ylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (85.0 mg, 0.13 mmol) (for preparation, see the following steps B, C, D, E and F), DMAP (64.0 mg, 0.53 mmol) and 4-

5 (acetylamino)benzenesulfonyl chloride (60.7 mg, 0.26 mmol) in MeCN (5 mL) were stirred for 8 h at room temperature. The reaction mixture was quenched with H₂O (3 mL). Upon evaporation, the residue was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 45.8 mg (63%); ¹HNMR (400 MHz, CD₃OD): δ

10 1.07 - 1.13 (m, 4 H), 1.14 - 1.21 (m, 1 H). 2.02 (s, 6 H), 2.14 (s, 3 H), 2.92 - 3.09 (m, 2 H), 3.27 (s, 3 H), 3.71 - 3.80 (m, 2 H), 3.95 (d, J=6.64 Hz, 2 H), 7.28 (dd, J=8.98, 1.95 Hz, 1 H), 7.41 - 7.46 (m, 1 H), 7.46 - 7.51 (m, 2 H), 7.57 (d, J=1.76 Hz, 1 H), 7.67 - 7.80 (m, 4 H), 7.91 - 8.02 (m, 1 H), 8.43 - 8.55 (m, 1 H); MS (ESI) (M+H)⁺: 562.0; Anal. Calcd for C₃₀H₃₅N₅O₄S + 1.20TFA + 0.40H₂O + 0.50 CH₃OH (721.61):

15 C, 54.75; H, 5.45; N, 9.70; Found: C, 54.76; H, 5.46; N, 9.76.

Step B. *N*-methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide



20 4-Aminomethylpyran (2.50 g, 21.7 mmol) was added to a mixture of *N*-(4-fluoro-3-nitrophenyl)-*N*-methylacetamide (4.61 g, 21.27 mmol) (for preparation, see Example 97, Step B) and sodium carbonate (5.10 g, 47.7 mmol) in EtOH (120 mL) at room temperature. The reaction mixture was heated for 3 days at 60 °C. Upon evaporation

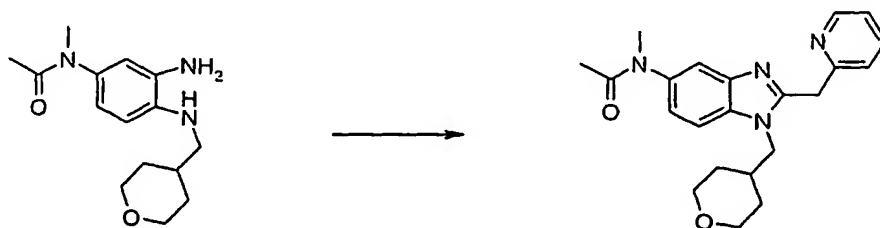
of ethanol, the residue was dissolved in EtOAc (400 mL), washed with H₂O (3x50 mL), saturated NaCl (3x50 mL), and dried over Na₂SO₄. After filtration and concentration, 6.62 g (100%) of the title compound was obtained as an orange-red solid. ¹H NMR (400 MHz, CDCl₃): δ 1.38 - 1.52 (m, 2 H), 1.72 - 1.81 (m, 2 H), 1.90 (s, 3 H), 1.93 - 2.02 (m, 1 H), 3.23 (s, 3 H), 3.23 - 3.27 (m, 2 H), 3.36 - 3.49 (m, 2 H), 4.01 - 4.07 (m, 2 H), 6.91 (d, *J*=9.18 Hz, 1 H), 7.29 (dd, *J*=9.08, 2.64 Hz, 1 H), 8.05 (d, *J*=2.34 Hz, 1 H), 8.22 (t, *J*=5.37 Hz, 1 H); MS (ESI) (M+H)⁺: 309.12.

Step C. *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide



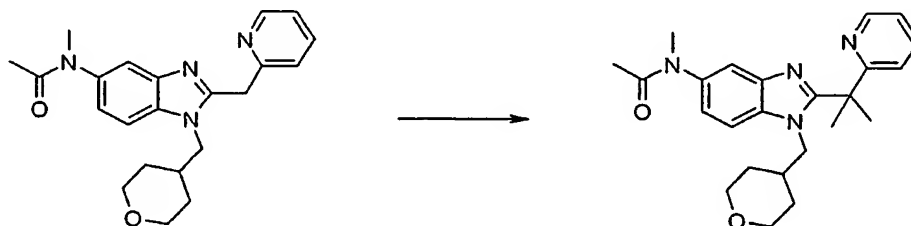
N-methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (5.39 g, 16.7 mmol) was hydrogenated in ethyl acetate (200 mL) catalyzed by 10% Pd/C (0.2 g) at 30-40 psi H₂ in Parr shaker for 18 h at room temperature. After filtration through celite and concentration, 6.0 g (100%) of a purple solid was obtained as HCl salt, which was used in the next step without purification. ¹H NMR (400 MHz, CD₃OD): δ 1.32 - 1.46 (m, 2 H), 1.78 - 1.84 (m, 2 H), 1.85 (s, 3 H), 1.91 - 2.06 (m, 1 H), 3.16 (d, *J*=6.83 Hz, 2 H), 3.20 (s, 3 H), 3.39 - 3.51 (m, 2 H), 3.94 - 4.03 (m, 2 H), 7.01 (d, *J*=8.59 Hz, 1 H), 7.12 (d, *J*=2.15 Hz, 1 H), 7.17 (dd, *J*=8.49, 4.39 Hz, 1 H); MS (ESI) (M+H)⁺: 278.7

Step D. *N*-methyl-*N*-[2-(pyridin-2-ylmethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide



Diisopropylethylamine (0.970 g, 7.50 mmol) was added into a solution of *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide hydrochloride (0.416 g, 1.33 mmol) and 2-pyridylacetic acid hydrochloride (0.286 g, 1.65 mmol) in DMF (15 mL) at 0 °C. Stirring for 20 min HATU (0.680 g, 1.80 mmol) was added. The reaction mixture was stirred for 4 h at room temperature, quenched with water (5 mL), concentrated to small volume, dissolved EtOAc (150 mL), washed with saturated NaCl (10 mL) and dried with anhydrous Na₂SO₄. After filtration and concentration, the residue was dissolved in acetic acid (20 mL) and heated for 18 h at 80 °C. Upon evaporation of the solvent, the residue was diluted with EtOAc (150 mL), washed with 2 *N* NaOH (10 mL) and saturated NaCl (2x10 mL), and dried over Na₂SO₄. After filtration and evaporation, the crude product was purified by MPLC using CH₂Cl₂/MeOH (10:1) on silica gel to give 0.31 g (61%) of a yellow solid as the title compound. MS (ESI) (M+H)⁺: 379.0.

Step E. *N*-methyl-*N*-[2-(1-methyl-1-pyridin-2-ylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide

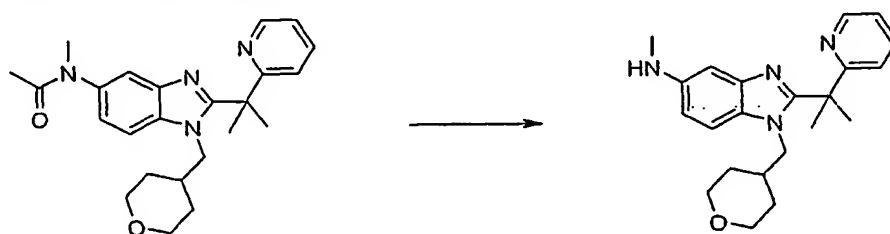


KHMDS (1.6 mL, 0.5 *M*, 0.8 mmol) was added to a solution of *N*-methyl-*N*-[2-(pyridin-2-ylmethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide (248.4 mg, 0.656 mmol) in THF (25 mL) at -78 °C. Stirring for 10 min, iodomethane (113.6 mg, 50 uL, 0.80 mmol) was added. The mixture was stirred for 30 min at -78 °C and 30 min at room temperature, then cooled down to -78 °C again. Another 1.2 equivalent KHMDS and iodomethane were added. The resulting mixture was stirred for 30 min at -78 °C and 45 min at room temperature, quenched with saturated NaHCO₃ (5 mL), and extracted with EtOAc (3x20 mL). The combined organic phases were washed with saturated NaHCO₃ (20 mL), brine (20 mL) and dried over Na₂SO₄. After filtration and concentration, the residue was purified by MPLC using EtOAc/MeOH (20:1) on silica gel to give 218.1 mg (90%) of the title

compound as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 1.02 - 1.12 (m, 2 H), 1.13 - 1.19 (m, 2 H), 1.19 - 1.27 (m, 1 H), 1.90 (s, 3 H), 1.97 (s, 6 H), 2.90 - 3.11 (m, 2 H), 3.31 (s, 3 H), 3.68 (d, $J=7.22$ Hz, 2 H), 3.81 (m, 2 H), 7.04 (dd, $J=8.49$, 2.05 Hz, 1 H), 7.18 - 7.32 (m, 3 H), 7.57 - 7.70 (m, 2 H), 8.53 - 8.70 (m, 1 H); MS (ESI)

5 (M+H) $^+$: 407.03.

Step F. *N*-methyl-2-(1-methyl-1-pyridin-2-ylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine

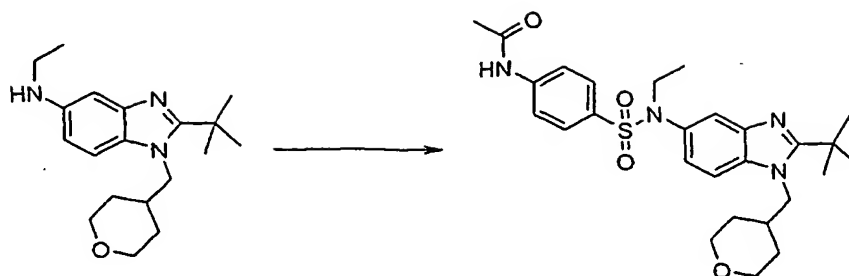


10 *N*-methyl-*N*-[2-(1-methyl-1-pyridin-2-ylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide (214.0 mg, 0.526 mmol) was dissolved in 5 mL of EtOH-2*N* HCl (3:2), and then heated at 120°C in a Personal Chemistry SmithSynthesizer microwave instrument for 1 h. After concentration and dried *in vacuo*, 331 mg (100%) of a grey white solid was obtained as the title product. ^1H

15 NMR (400 MHz, DMSO- D_6): δ 0.86 - 1.08 (m, 4 H), 1.94 (s, 6 H), 1.96 - 2.03 (m, 1 H), 2.71 - 2.92 (m, 5 H), 3.55 - 3.70 (m, 2 H), 3.86 (d, $J=5.47$ Hz, 2 H), 7.31 - 7.48 (m, 2 H), 7.69 (d, $J=7.42$ Hz, 1 H), 7.74 - 7.84 (m, 1 H), 7.93 (t, $J=8.30$ Hz, 1 H), 8.48 (d, $J=4.10$ Hz, 2 H); MS (ESI) (M+H) $^+$: 365.04.

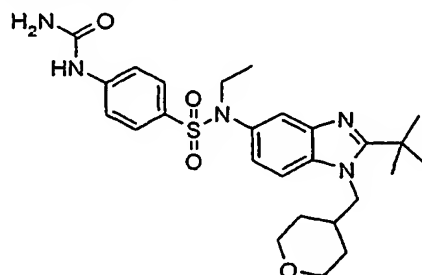
20 Example 104

N-(4-[[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](ethyl)amino]sulfonyl]phenyl)acetamide



2-*tert*-butyl-*N*-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (52.8 mg, 0.15 mmol) (for preparation, see Example 71), DMAP (73.3 mg, 0.60 mmol) and 4-(acetylamino)benzenesulfonyl chloride (70.1 mg, 0.30 mmol) in MeCN (5 mL) were stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (100 mL), washed with saturated NaHCO₃ (10 mL) and saturated NaCl (10 mL), and dried over Na₂SO₄. Upon evaporation, the residue was purified by MPLC using EtOAc/MeOH (20:1) on silica gel to give 60.3 mg (78%) of a white solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 1.07 (t, J=7.13 Hz, 3 H), 1.51 - 1.64 (m, 4 H), 1.68 (s, 9 H), 2.15 (s, 3 H), 2.29 - 2.47 (m, 1 H), 3.32 - 3.42 (m, 2 H), 3.72 (q, J=7.22 Hz, 2 H), 3.90 - 4.01 (m, 2 H), 4.53 (d, J=7.42 Hz, 2 H), 7.25 (dd, J=8.98, 1.95 Hz, 1 H), 7.47 - 7.55 (m, 3 H), 7.66 - 7.78 (m, 2 H), 7.90 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 513.0; Anal. Calcd for C₂₇H₃₆N₄O₄S+ 1.30 TFA+0.30 CH₃OH (670.52): C, 53.56; H, 5.79; N, 8.36; Found: C, 53.66; H, 5.75; N, 8.10..

Example 105
4-[(aminocarbonyl)amino]-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethylbenzenesulfonamide



Following the procedure as in Example 104, using 2-*tert*-butyl-*N*-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (52.8 mg, 0.15 mmol), DMAP (73.3 mg, 0.60 mmol) and 4-[(aminocarbonyl)amino]benzenesulfonyl chloride (70.3 mg, 0.30 mmol) in MeCN (5 mL), the crude product was purified by

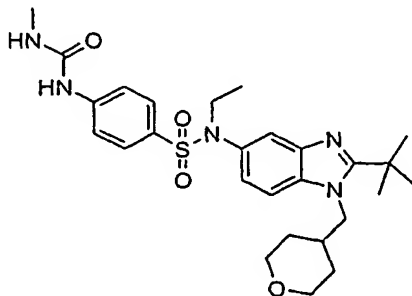
5 MPLC using EtOAc/MeOH (20:1) on silica gel to give 59.9 mg (78%) of a white solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 1.06 (t, J=7.13 Hz, 3 H), 1.51 - 1.64 (m, 4 H), 1.68 (s, 9 H), 2.29 - 2.48 (m, 1 H), 3.31 - 3.43 (m, 2 H), 3.71 (q, J=7.03 Hz, 2 H), 3.86 - 4.01 (m, 2 H), 4.52 (d, J=7.62 Hz, 2 H), 7.26 (dd, J=8.88, 1.85 Hz, 1 H), 7.41 - 7.49 (m, 3 H), 7.51 - 7.59 (m, 2 H), 7.90 (d, J=8.98 Hz, 1 H);

10 MS (ESI) (M+H)⁺: 514.0; Anal. Calcd for C₂₆H₃₅N₅O₄S+ 1.30 TFA+0.40 CH₃OH (674.71): C, 51.63; H, 5.66; N, 10.38; Found: C, 51.65; H, 5.63; N, 10.38.

Example 106

N-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethyl-4-[[[(methylamino)carbonyl]amino]benzenesulfonamide

15



Following the procedure as in Example 104, using 2-*tert*-butyl-*N*-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (52.8 mg, 0.15 mmol), DMAP (73.3 mg, 0.60 mmol) and 4-[[[(methylamino)carbonyl]amino]benzenesulfonyl chloride (74.6 mg, 0.30 mmol) in MeCN (5 mL), the crude product was purified by MPLC using EtOAc/MeOH (20:1) on silica gel to give 63.2 mg (80%) of a white solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 1.06 (t, J=7.13 Hz, 3 H), 1.50 - 1.64 (m, 4 H), 1.68 (s, 9 H), 2.29 - 2.46 (m, 1 H), 2.77 (s, 3 H), 3.31 - 3.41 (m, 2 H), 3.71 (q, J=7.16 Hz, 2 H), 3.91 - 4.00 (m, 2 H), 4.52 (d, J=7.42 Hz, 2 H), 7.26 (dd, J=8.88, 2.05 Hz, 1 H), 7.40 - 7.46 (m, 2 H), 7.48 (d, J=1.76 Hz, 1 H), 7.50 - 7.55 (m, 2 H), 7.89 (d, J=8.98 Hz, 1 H);

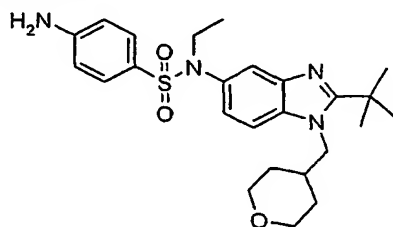
20

25

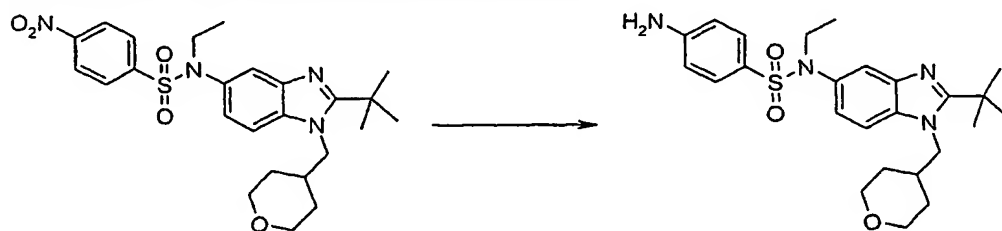
MS (ESI) (M+H)⁺: 528.0; Anal. Calcd for C₂₇H₃₇N₅O₄S+ 1.40 TFA+0.50 H₂O (696.33): C, 51.40; H, 5.70; N, 10.06; Found: C, 51.38 ; H, 5.69; N, 10.09.

Example 107

- 5 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethylbenzenesulfonamide



Step A. 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethylbenzenesulfonamide

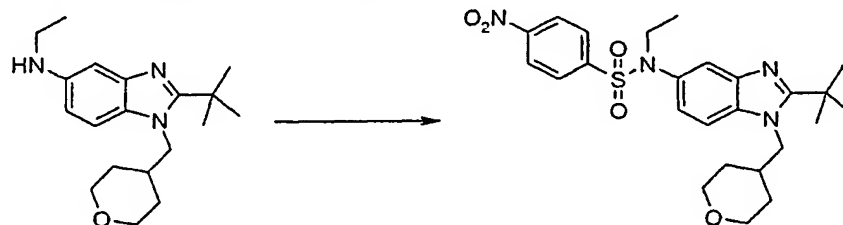


10

- N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethyl-4-nitrobenzenesulfonamide (399.6 mg, 0.798 mmol) (for preparation, see the following step B) was hydrogenated in ethyl acetate (50 mL) catalyzed by 10% Pd/C (100 mg) at 30-40 psi H₂ in Parr shaker for 6 h at room temperature. After filtration through celite and concentration, 457.9 mg (100%) of a white solid was obtained. Small amounts of the crude product was purified by reversed-phase HPLC using 20-50% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. ¹HNMR (400 MHz, CD₃OD): δ 1.04 (t, J=7.13 Hz, 3 H), 1.49 - 1.65 (m, 4 H), 1.68 (s, 9 H), 2.25 - 2.55 (m, 1 H), 3.32 - 3.43 (m, 2 H), 3.66 (q, J=7.03 Hz, 2 H), 3.88 - 4.04 (m, 2 H), 4.53 (d, J=7.42 Hz, 2 H), 6.50 - 6.69 (m, 2 H), 7.19 - 7.26 (m, 2 H), 7.28 (dd, J=8.98, 1.95 Hz, 1 H), 7.50 (d, J=1.76 Hz, 1 H), 7.90 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 471.0; Anal. Calcd for C₂₅H₃₄N₄O₃S+ 1.80
- 15
- 20

TFA+0.30 H₂O (681.29): C, 50.42; H, 5.39; N, 8.22; Found: C, 50.38 ; H, 5.21; N, 8.44.

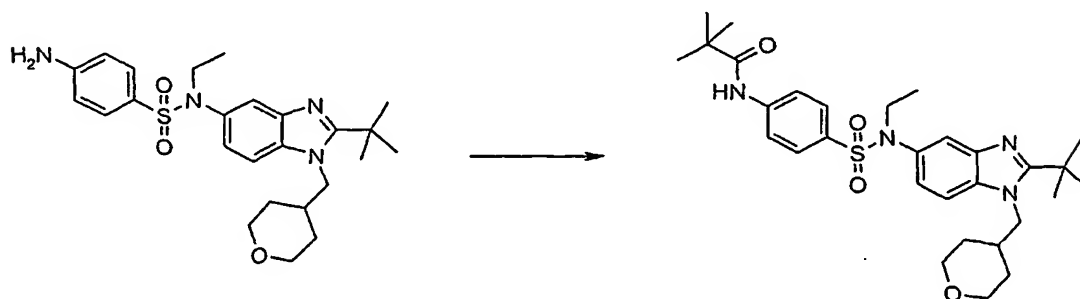
Step B. *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethyl-4-nitrobenzenesulfonamide



Following the procedure as in Example 104, using 2-*tert*-butyl-*N*-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (354.1 mg, 1.01 mmol) DMAP (491.7 mg, 4.03 mmol) and 4-nitrobenzenesulfonyl chloride (445.9 mg, 2.01 mmol) in MeCN (20 mL), the crude product was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 399.6 mg (80%) of a yellow solid as the title compound. MS (ESI) (M+H)⁺: 501.0.

Example 108

***N*-(4-[[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](ethyl)amino]sulfonyl]phenyl)-2,2-dimethylpropanamide**

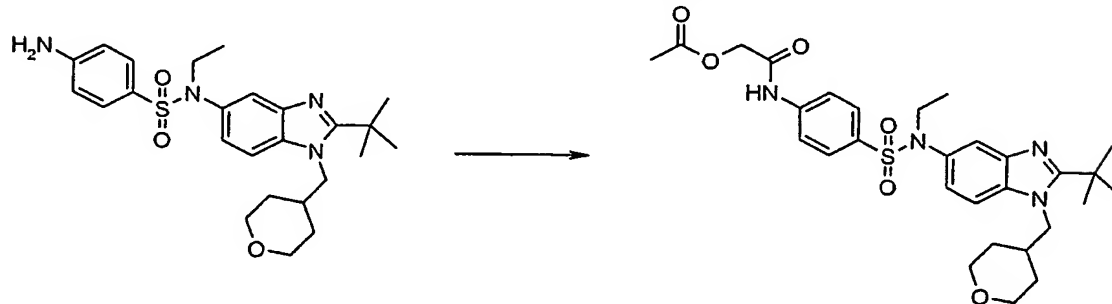


4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethylbenzenesulfonamide (56.7 mg, 0.10 mmol) (for preparation, see the step A in Example 107), DMAP (48.9 mg, 0.40 mmol) and trimethylacetyl chloride (24.6 mg,

- 0.20 mmol) in MeCN (5 mL) were stirred for 4 h at room temperature. The reaction mixture was diluted with EtOAc (100 mL), washed with saturated NaHCO₃ (10 mL) and saturated NaCl (10 mL), and dried over Na₂SO₄. Upon evaporation, the residue was purified by reversed-phase HPLC using 20-70% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 41.3 mg (74%); ¹HNMR (400 MHz, CD₃OD): δ 1.07 (t, J=7.13 Hz, 3 H), 1.29 (s, 9 H), 1.52 - 1.63 (m, 4 H), 1.67 (s, 9 H), 2.31 - 2.44 (m, 1 H), 3.31 - 3.41 (m, 2 H), 3.72 (q, J=7.03 Hz, 2 H), 3.95 (m, 2 H), 4.51 (d, J=7.62 Hz, 2 H), 7.24 (dd, J=8.98, 1.95 Hz, 1 H), 7.47 (d, J=1.95 Hz, 1 H), 7.48 - 7.56 (m, 2 H), 7.73 - 7.82 (m, 2 H), 7.88 (d, J=8.98 Hz, 1 H), 9.39 (s, 1 H); MS (ESI) (M+H)⁺: 555.0; Anal. Calcd for C₃₀H₄₃N₃O₄S + 1.80 TFA + 0.30 H₂O (765.40): C, 52.73; H, 5.85; N, 7.32; Found: C, 52.67; H, 5.75; N, 7.45.

Example 109

- 2-[(4-[[[2-*tert*-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](ethyl)amino]sulfonyl]phenyl)amino]-2-oxoethyl acetate

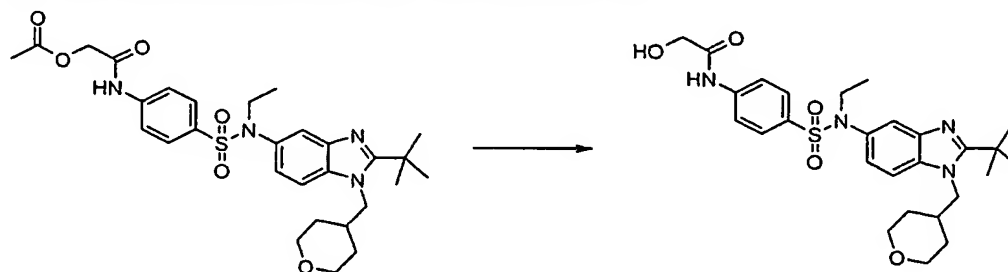


- Following the procedure for Example 108, using 4-amino-N-[2-*tert*-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-ethylbenzenesulfonamide (113.4 mg, 0.20 mmol) (for preparation, see the step A in Example 107), DMAP (97.7 mg, 0.80 mmol) and 2-chloro-2-oxoethyl acetate (54.6 mg, 0.40 mmol) in MeCN (10 mL), the crude product was purified by MPLC using EtOAc on silica gel to give 102.6 mg (90%) of a white solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 1.07 (t, J=7.13 Hz, 3 H), 1.51 - 1.64 (m, 4 H), 1.67 (s, 9 H), 2.16 (s, 3 H), 2.30 - 2.45 (m, 1 H), 3.32 - 3.44 (m, 2 H), 3.73 (q, J=7.23 Hz, 2 H), 3.84 - 4.04 (m, 2 H), 4.51 (d, J=7.42 Hz, 2 H), 4.69 (s, 2 H), 7.24 (dd, J=8.98,

1.95 Hz, 1 H), 7.47 (d, $J=1.76$ Hz, 1 H), 7.50 - 7.57 (m, 2 H), 7.68 - 7.79 (m, 2 H), 7.89 (d, $J=8.98$ Hz, 1 H); MS (ESI) $(M+H)^+$: 571.0; Anal. Calcd for $C_{29}H_{38}N_4O_6S^+$ 0.90 TFA (673.33): C, 54.94; H, 5.82; N, 8.32; Found: C, 54.95; H, 5.79; N, 8.13.

5 Example 110

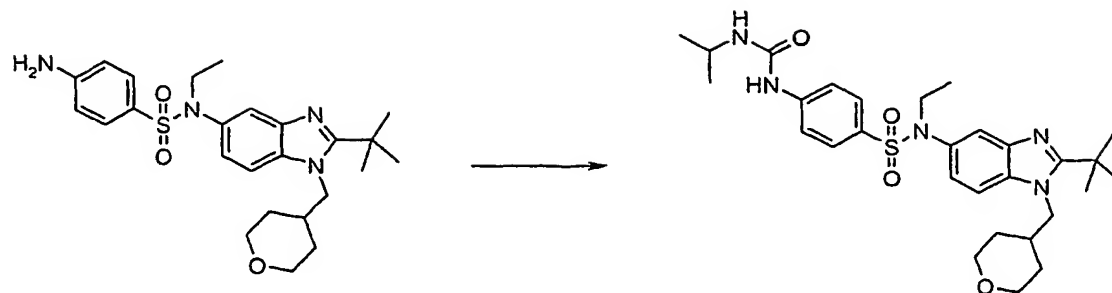
N-(4-[[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](ethyl)amino]sulfonyl]phenyl)-2-hydroxyacetamide



- 10 2-[(4-[[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](ethyl)amino]sulfonyl]phenyl)amino]-2-oxoethyl acetate (70.3 mg, 0.123 mmol) (for preparation, see the Example 109) and a drop of sodium methoxide (25% in MeOH) in MeOH (5 mL) was stirred overnight at room temperature. After evaporation, the crude product was purified by reversed-phase HPLC using 10-50%
 15 CH_3CN/H_2O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 58.5 mg (90%); 1H NMR (400 MHz, CD_3OD): δ 1.07 (t, $J=7.13$ Hz, 3 H), 1.51 - 1.64 (m, 4 H), 1.68 (s, 9 H), 2.25 - 2.48 (m, 1 H), 3.31 - 3.41 (m, 2 H), 3.73 (q, $J=7.16$ Hz, 2 H), 3.95 (m, 2 H), 4.13 (s, 2 H), 4.52 (d, $J=7.42$ Hz, 2 H), 7.25 (dd, $J=8.98, 1.95$ Hz, 1 H), 7.49 (d, $J=1.76$ Hz, 1 H), 7.50 - 7.58 (m, 2 H), 7.78 - 7.85 (m, 2 H), 7.89 (d, $J=8.98$ Hz, 1 H); MS (ESI) $(M+H)^+$: 529.0; Anal. Calcd for $C_{27}H_{36}N_4O_5S^+$ 1.50 TFA + 0.20 H_2O + 0.30 CH_3CN (715.63): C, 51.36; H, 5.47; N, 8.42; Found: C, 51.35; H, 5.47; N, 8.35.

Example 111

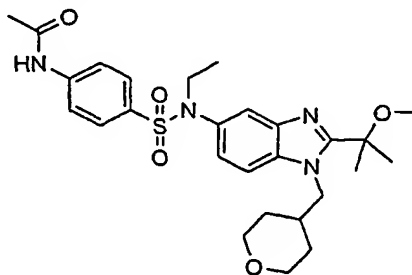
- 25 *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethyl-4-[(isopropylamino)carbonyl]aminobenzenesulfonamide



- 4-Amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethylbenzenesulfonamide (56.7 mg, 0.1 mmol) (for preparation, see the step A in
- 5 Example 107) and 2-isocyanatopropane (0.1 mL) in DCE (5 mL) was heated overnight at 80 °C. After evaporation, the crude product was purified by reversed-phase HPLC using 20-50% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 39.5 mg (71%); ¹HNMR (400 MHz, CD₃OD): δ 1.06 (t, J=7.13 Hz, 3 H), 1.18 (d, J=6.64 Hz, 6 H), 1.51 - 1.63 (m, 4 H),
- 10 1.68 (s, 9 H), 2.27 - 2.42 (m, 1 H), 3.32 - 3.42 (m, 2 H), 3.70 (q, J=7.03 Hz, 2 H), 3.83 - 3.92 (m, 1 H), 3.92 - 3.99 (m, 2 H), 4.52 (d, J=7.42 Hz, 2 H), 7.25 (dd, J=8.88, 2.05 Hz, 1 H), 7.40 - 7.46 (m, 2 H), 7.47 (d, J=1.95 Hz, 1 H), 7.48 - 7.54 (m, 2 H), 7.89 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 556.0; Anal. Calcd for C₂₉H₄₁N₅O₄S+ 1.80 TFA+0.20 H₂O+0.50 CH₃CN (785.12): C, 51.40; H, 5.74; N, 9.81; Found: C, 51.40;
- 15 H, 5.72; N, 9.79.

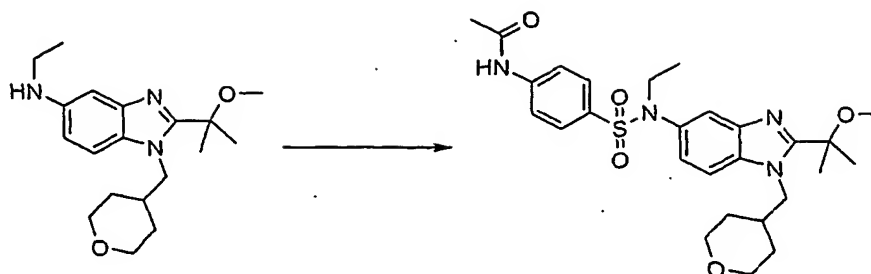
Example 112

N-[4-((ethyl[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino)sulfonyl)phenyl]acetamide



20

Step A. *N*-[4-((ethyl[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino)sulfonyl)phenyl]acetamide



Following the procedure as in Example 104, using *N*-ethyl-2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (50.0 mg, 0.136 mmol) (for preparation, see the following steps B, C and D), DMAP (64.5 mg, 0.50 mmol) and 4-(acetlamino)benzenesulfonyl chloride (61.2 mg, 0.26 mmol) in MeCN (5 mL), the crude product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 42.0 mg (58%); ¹HNMR (400 MHz, CD₃OD): δ 1.06 (t, J=7.03 Hz, 3 H), 1.42 - 1.61 (m, 4 H), 1.80 (s, 6 H), 2.15 (s, 3 H), 2.31 - 2.46 (m, 1 H), 3.34 (s, 3 H), 3.35 - 3.43 (m, 2 H), 3.71 (q, J=7.23 Hz, 2 H), 3.89 - 4.02 (m, 2 H), 4.53 (d, J=7.42 Hz, 2 H), 7.20 (dd, J=8.88, 1.85 Hz, 1 H), 7.43 (d, J=1.76 Hz, 1 H), 7.48 - 7.57 (m, 2 H), 7.68 - 7.76 (m, 2 H), 7.81 (d, J=8.79 Hz, 1 H); MS (ESI) (M+H)⁺: 529.0; Anal. Calcd for C₂₇H₃₆N₄O₅S+ 1.20 TFA+0.20 H₂O (669.11): C, 52.78; H, 5.66; N, 8.37; Found: C, 52.80; H, 5.59; N, 8.51.

15

Step B. *N*-ethyl-*N*-[2-(1-hydroxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide

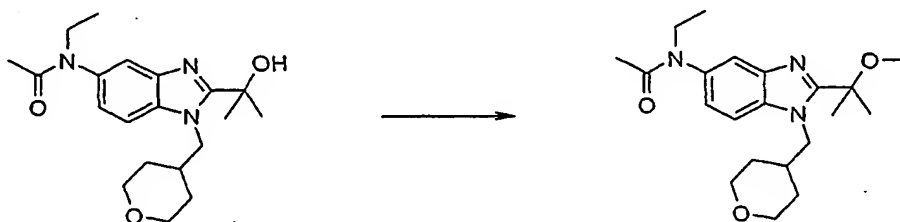


Diisopropylethylamine (0.558 g, 4.32 mmol) was added into a solution of *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-ethylacetamide (0.841 g, 2.88 mmol) and 2-hydroxy-2-methylpropanoic acid (0.330 g, 3.17 mmol) in DMF (40 mL) at 0 °C. Stirring for 30 min, HATU (1.31 g, 3.46 mmol) was added. The reaction mixture was stirred for overnight at room temperature and quenched with

20

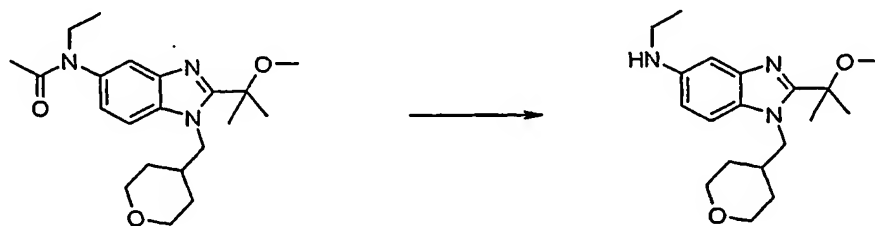
water (5 mL). After concentration, the residue was dissolved in acetic acid (50 mL) in sealed tubes. The solutions were heated at 140°C using a Personal Chemistry Smith Synthesizer microwave instrument for 35 min. Upon evaporation of the solvent, the residue was diluted with EtOAc (100 mL), washed with 2 N NaOH (10 mL) and
 5 saturated NaCl (2x10 mL), and dried over Na₂SO₄. After filtration and evaporation, 1.78 g (purity >43%) of the crude product was obtained, which was used directly for next step without purification. MS (ESI) (M+H)⁺: 360.04.

Step C. *N*-ethyl-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide
 10



Sodium hydride (0.35 g, 60%, 8.64 mmol) was added in portions to a solution of *N*-ethyl-*N*-[2-(1-hydroxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide (1.78 g of the above crude product, 2.88 mmol) in THF
 15 (100 mL) at 0 °C. Stirring for 20 min, iodomethane (1.23 g, 8.64 mmol) was added. The reaction mixture was stirred overnight at room temperature, quenched with saturated NH₄Cl (20 mL) and diluted with EtOAc (100 mL), washed with saturated NaCl (2x20 mL) and dried over Na₂SO₄. After filtration and concentration, the residue was purified by MPLC using EtOAc/MeOH (20:1) on silica gel to give 0.423
 20 g (39%) of a grey white solid as the title compound. MS (ESI) (M+H)⁺: 374.03.

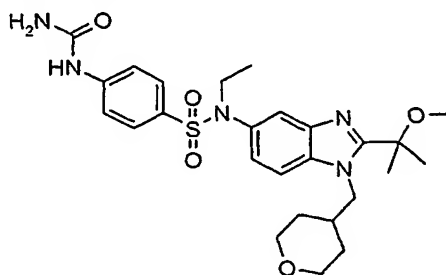
Step D. *N*-ethyl-2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine



N-ethyl-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide (422.5 mg, 1.13 mmol) was dissolved in 15 mL of EtOH-2*N* HCl (3:2), and then heated at 120°C in a Personal Chemistry SmithSynthesizer microwave instrument for 3.5 h. After concentration and dried *in vacuo*, 441.9 mg (100%) of a light brown solid was obtained as the title product. MS (ESI) (M+H)⁺: 332.04.

Example 113

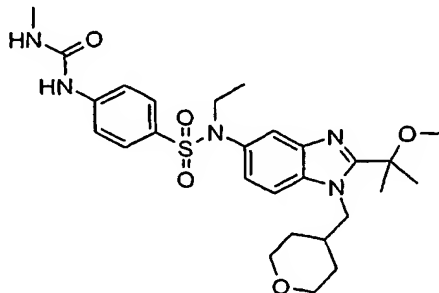
4-[(aminocarbonyl)amino]-*N*-ethyl-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



Following the procedure for the step A in Example 105, using *N*-ethyl-2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (50.0 mg, 0.136 mmol) (for preparation, see the steps B, C and D in example 15), DMAP (64.5 mg, 0.50 mmol) and 4-[(aminocarbonyl)amino]benzenesulfonyl chloride (64.5 mg, 0.26 mmol) in MeCN (5 mL), the crude product was purified by reversed-phase HPLC using 10-45% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 31.1 mg (43%); ¹HNMR (400 MHz, CD₃OD): δ 1.06 (t, J=7.13 Hz, 3 H), 1.50 - 1.58 (m, 4 H), 1.81 (s, 6 H), 2.29 - 2.48 (m, 1 H), 3.35 (s, 3 H), 3.36 - 3.43 (m, 2 H), 3.70 (q, J=7.03 Hz, 2 H), 3.89 - 4.02 (m, 2 H), 4.54 (d, J=7.22 Hz, 2 H), 7.22 (dd, J=8.98, 1.95 Hz, 1 H), 7.40 - 7.49 (m, 3 H), 7.51 - 7.58 (m, 2 H), 7.77 - 7.90 (m, 1 H); MS (ESI) (M+H)⁺: 530.0; Anal. Calcd for C₂₆H₃₅N₅O₅S+ 1.20 TFA+1.10 H₂O +0.10 CH₃OH (689.51): C, 49.65; H, 5.67; N, 10.16; Found: C, 49.67; H, 5.67; N, 10.19.

Example 114

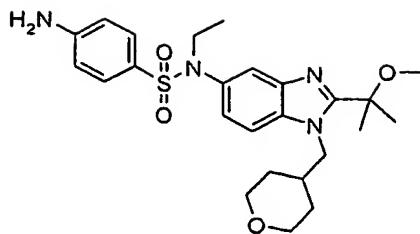
***N*-ethyl-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-[[[(methylamino)carbonyl]amino]benzenesulfonamide**



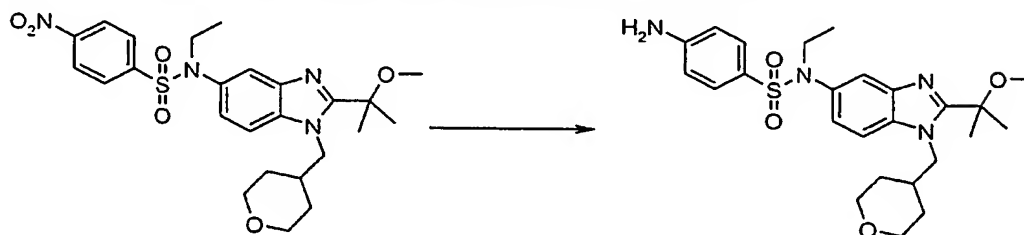
- 5 Following the procedure for the step A in Example 105, using *N*-ethyl-2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (50.0 mg, 0.136 mmol) (for preparation, see the steps B, C and D in example 112), DMAP (64.5 mg, 0.50 mmol) and 4-
 10 [[[(methylamino)carbonyl]amino]benzenesulfonyl chloride (62.0 mg, 0.26 mmol) in MeCN (5 mL), the crude product was purified by reversed-phase HPLC using 10-45% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 36.9 mg (50%); ¹HNMR (400 MHz, CD₃OD): δ 1.06 (t, J=7.13 Hz, 3 H), 1.51 - 1.59 (m, 4 H), 1.81 (s, 6 H), 2.31 - 2.47 (m, 1 H), 2.77 (s, 3 H), 3.35 (s, 3 H), 3.36 - 3.41 (m, 2 H), 3.70 (q, J=7.16 Hz, 2 H), 3.91 - 3.99 (m, 2
 15 H), 4.54 (d, J=7.42 Hz, 2 H), 7.20 - 7.25 (m, 1 H), 7.44 (d, J=2.15 Hz, 1 H), 7.44 - 7.48 (m, 2 H), 7.50 - 7.56 (m, 2 H), 7.85 (d, J=9.18 Hz, 1 H); MS (ESI) (M+H)⁺: 544.0; Anal. Calcd for C₂₇H₃₇N₅O₅S + 0.80 TFA + 0.50 H₂O (643.92): C, 53.35; H, 6.07; N, 10.88; Found: C, 53.25; H, 6.05; N, 10.99.

Example 115

4-amino-*N*-ethyl-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



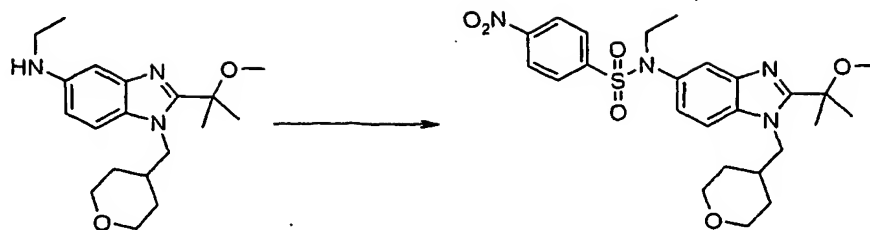
Step A. 4-amino-*N*-ethyl-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



5

Following the procedure for the step A in Example 107, using *N*-ethyl-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-nitrobenzenesulfonamide (276.0 mg, 0.798 mmol) (for preparation, see the following step B) and 10% Pd/C (50 mg) in ethyl acetate (50 mL), 287.7 mg (100%) of a white solid was obtained. Small amounts of the crude product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. ¹HNMR (400 MHz, CD₃OD): δ 1.03 (t, J=7.13 Hz, 3 H), 1.50 - 1.58 (m, 4 H), 1.81 (s, 6 H), 2.31 - 2.48 (m, 1 H), 3.35 (s, 3 H), 3.36 - 3.42 (m, 2 H), 3.65 (q, J=7.03 Hz, 2 H), 3.90 - 3.99 (m, 2 H), 4.54 (d, J=7.42 Hz, 2 H), 6.60 - 6.66 (m, 2 H), 7.21 - 7.27 (m, 3 H), 7.44 (d, J=1.95 Hz, 1 H), 7.82 (d, J=8.79 Hz, 1 H); MS (ESI) (M+H)⁺: 487.0; Anal. Calcd for C₂₅H₃₄N₄O₄S+1.50 TFA (657.67): C, 51.14; H, 5.44; N, 8.52; Found: C, 51.31; H, 5.44; N, 8.40.

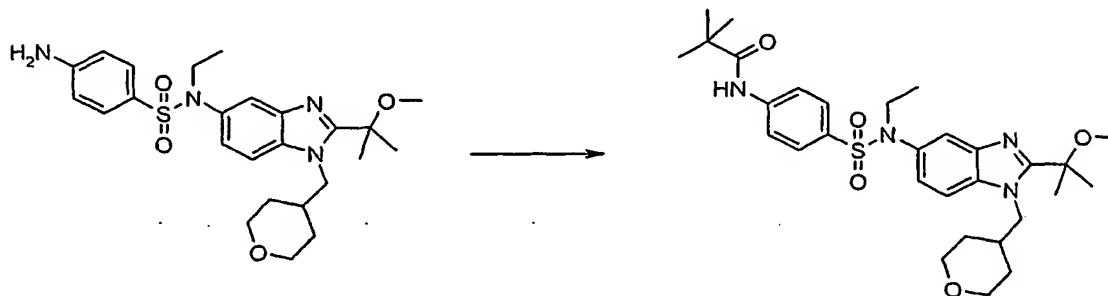
Step B. *N*-ethyl-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-nitrobenzenesulfonamide



- Following the procedure as in Example 104, using *N*-ethyl-2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (248.2 mg, 0.675 mmol) (for preparation, see the steps B, C and D in example 112), DMAP (329.9 mg, 2.70 mmol) and 4-nitrobenzenesulfonyl chloride (299.0 mg, 1.35 mmol) in MeCN (15 mL), the crude product was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 276.0 mg (79%) of a yellow solid as the title compound. MS (ESI) ($M+H$)⁺: 517.00.

10 Example 116

N-[4-({ethyl[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]-2,2-dimethylpropanamide

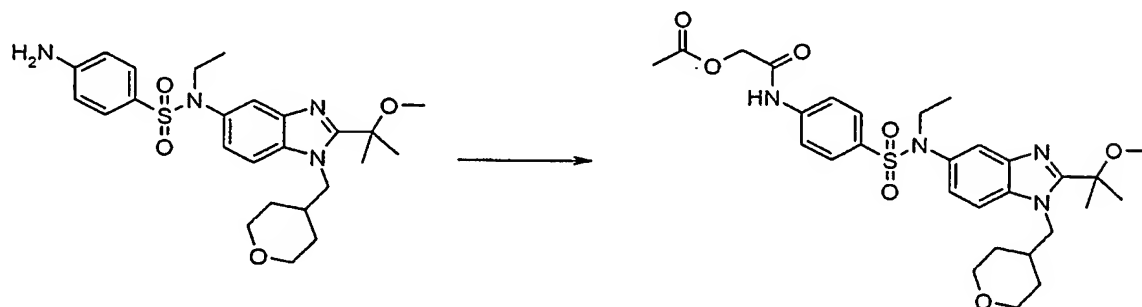


- Following the procedure for Example 108, using 4-amino-*N*-ethyl-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (51.5 mg, 0.095 mmol) (for preparation, see the step A in Example 115), DMAP (50.0 mg, 0.409 mmol) and trimethylacetyl chloride (24.6 mg, 0.20 mmol) in MeCN (5 mL), the crude product was purified by reversed-phase HPLC using 20-60% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 45.8 mg (85%); ¹HNMR (400 MHz, CD₃OD): δ 1.06 (t, *J*=7.13 Hz, 3 H), 1.30 (s, 9 H), 1.49 - 1.60 (m, 4 H), 1.80 (s, 6 H), 2.32 -

2.46 (m, 1 H), 3.34 (s, 3 H), 3.35 - 3.42 (m, 2 H), 3.71 (q, $J=7.03$ Hz, 2 H), 3.90 - 4.00 (m, 2 H), 4.53 (d, $J=7.42$ Hz, 2 H), 7.20 (dd, $J=8.98, 1.95$ Hz, 1 H), 7.42 (d, $J=1.76$ Hz, 1 H), 7.48 - 7.55 (m, 2 H), 7.75 - 7.81 (m, 2 H), 7.82 (s, 1 H); MS (ESI) ($M+H$)⁺: 571.00; Anal. Calcd for $C_{30}H_{42}N_4O_5S + 1.20$ TFA + 0.80 H_2O (722.00): C, 53.90; H, 6.25; N, 7.76; Found: C, 53.93; H, 6.25; N, 7.67.

Example 117

2-([4-({ethyl[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]amino}sulfonyl)phenyl]amino)-2-oxoethyl acetate



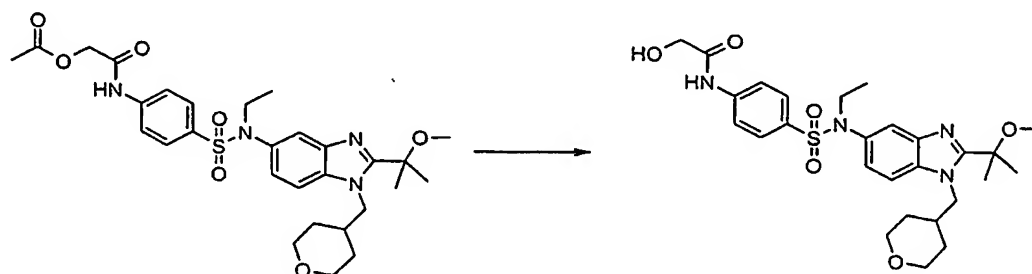
10

Following the procedure for Example 108, using 4-amino-*N*-ethyl-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]benzenesulfonamide (100.0 mg, 0.185 mmol) (for preparation, see the step A in Example 115), DMAP (97.7 mg, 0.80 mmol) and 2-chloro-2-oxoethyl acetate (54.6 mg, 0.40 mmol) in MeCN (10 mL), the crude product was purified by MPLC using Hex/EtOAc on silica gel to give 68.7 mg (63%) of a light yellow solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 1.06 (t, $J=7.13$ Hz, 3 H), 1.48 - 1.56 (m, 4 H), 1.76 (s, 6 H), 2.17 (s, 3 H), 2.30 - 2.46 (m, 1 H), 3.28 (s, 3 H), 3.32 - 3.42 (m, 2 H), 3.70 (q, $J=7.23$ Hz, 2 H), 3.85 - 4.04 (m, 2 H), 4.47 (d, $J=7.62$ Hz, 2 H), 4.70 (s, 2 H), 7.11 (dd, $J=8.79, 1.95$ Hz, 1 H), 7.33 (d, $J=1.95$ Hz, 1 H), 7.50 - 7.58 (m, 2 H), 7.68 (d, $J=8.79$ Hz, 1 H), 7.72 - 7.79 (m, 2 H); MS (ESI) ($M+H$)⁺: 587.0; Anal. Calcd for $C_{29}H_{38}N_4O_7S + 0.70$ TFA + 3.10 H_2O + 0.90 CH_3CN (759.32): C, 50.93; H, 6.32; N, 9.04; Found: C, 50.90; H, 6.26; N, 9.05.

25

Example 118

N-[4-({ethyl[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]-2-hydroxyacetamide



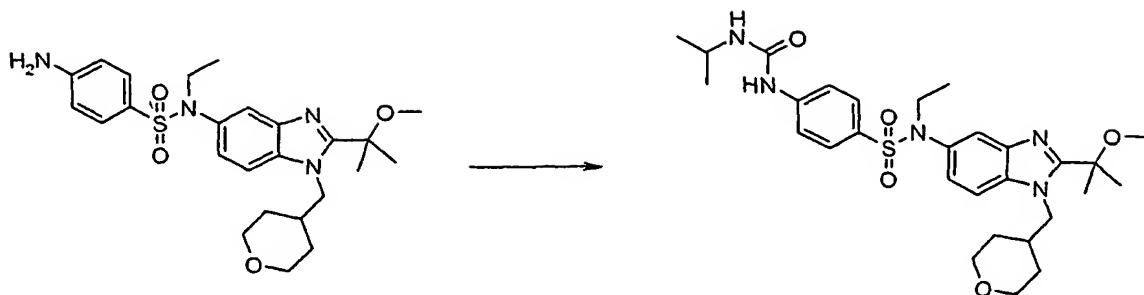
5

Following the procedure for Example 110, using 2-{{4-({ethyl[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]amino}-2-oxoethyl acetate (46.3 mg, 0.0789 mmol) (for preparation, see the Example 116) and a drop of sodium methoxide (25% in MeOH) in MeOH (5 mL), the crude product was purified by reversed-phase HPLC using 10-45% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 27.4 mg (64%); ¹HNMR (400 MHz, CD₃OD): δ 1.07 (t, J=7.13 Hz, 3 H), 1.50 - 1.56 (m, 4 H), 1.80 (s, 6 H), 2.32 - 2.46 (m, 1 H), 3.34 (s, 3 H), 3.35 - 3.41 (m, 2 H), 3.72 (q, J=7.03 Hz, 2 H), 3.91 - 3.99 (m, 2 H), 4.13 (s, 2 H), 4.53 (d, J=7.42 Hz, 2 H), 7.20 (dd, J=8.98, 1.95 Hz, 1 H), 7.44 (d, J=1.76 Hz, 1 H), 7.51 - 7.58 (m, 2 H), 7.79 - 7.85 (m, 3 H); MS (ESI) (M+H)⁺: 545.0; Anal. Calcd for C₂₇H₃₆N₄O₆S+ 1.30 TFA+0.50 H₂O (701.91): C, 50.65; H, 5.50; N, 7.98; Found: C, 50.61; H, 5.50; N, 8.12.

20

Example 119

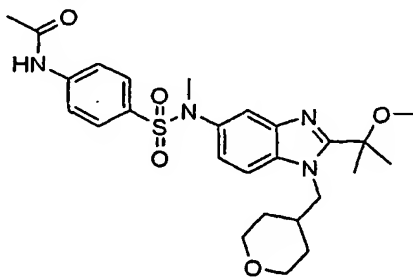
N-ethyl-4-{{[(isopropylamino)carbonyl]amino}-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



Following the procedure for Example 111, using 4-amino-*N*-ethyl-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (45.7 mg, 0.0845 mmol) (for preparation, see the step A in
 5 Example 114) and 2-isocyanatopropane (0.2 mL) in DCE (5 mL), the crude product was purified by reversed-phase HPLC using 20-50% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 17.1 mg (35%); ¹HNMR (400 MHz, CD₃OD): δ 1.05 (t, J=7.13 Hz, 3 H), 1.18 (d, J=6.44
 10 Hz, 6 H), 1.50 - 1.57 (m, 4 H), 1.79 (s, 6 H), 2.31 - 2.46 (m, 1 H), 3.33 (s, 3 H), 3.35 - 3.43 (m, 2 H), 3.69 (q, J=7.03 Hz, 2 H), 3.84 - 3.92 (m, 1 H), 3.92 - 3.99 (m, 2 H), 4.52 (dd, J=7.42 Hz, 2 H), 7.18 (dd, J=8.98, 1.95 Hz, 1 H), 7.41 (d, J=1.76 Hz, 1 H), 7.42 - 7.48 (m, 2 H), 7.48 - 7.56 (m, 2 H), 7.79 (d, J=8.79 Hz, 1 H); MS (ESI) (M+H)⁺: 572.0; Anal. Calcd for C₂₉H₄₁N₅O₅S+ 1.60 TFA+0.40 H₂O (761.39): C, 50.80; H, 5.75; N, 9.20; Found: C, 50.83; H, 5.77; N, 9.01.

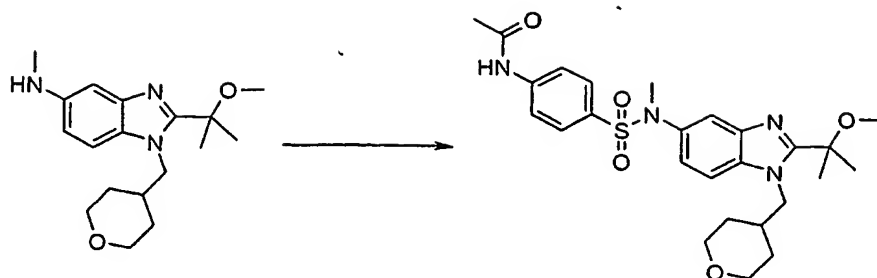
Example 120

N-(4-{[[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide



20

Step A. *N*-(4-{[[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide



Following the procedure as in Example 104, using 2-(1-methoxy-1-methylethyl)-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (77.8 mg, 0.15 mmol) (for preparation, see the following steps B, C and D), DMAP (73.3 mg, 0.60 mmol) and 4-(acetylamino)benzenesulfonyl chloride (68.9 mg, 0.30 mmol) in MeCN (10 mL), the crude product was purified by MPLC using EtOAc/MeOH (20:1) on silica gel to give 55.7 mg (72%) of a white solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 1.49 - 1.62 (m, 4 H), 1.83 (s, 6 H), 2.14 (s, 3 H), 2.32 - 2.46 (m, 1 H), 3.26 (s, 3 H), 3.32 - 3.37 (m, 2 H), 3.38 (s, 3 H), 3.90 - 4.00 (m, 2 H), 4.57 (d, *J*=7.42 Hz, 2 H), 7.33 (dd, *J*=8.98, 1.95 Hz, 1 H), 7.43 - 7.50 (m, 2 H), 7.54 (d, *J*=1.76 Hz, 1 H), 7.68 - 7.76 (m, 2 H), 7.89 (d, *J*=8.98 Hz, 1 H); MS (ESI) (*M*+*H*)⁺: 515.0; Anal. Calcd for C₂₆H₃₄N₄O₅S+ 1.3 HCl +0.4 CH₃OH (574.86): C, 55.16, H, 6.47, N, 9.75; Found: C, 55.25; H, 6.38; N, 9.58.

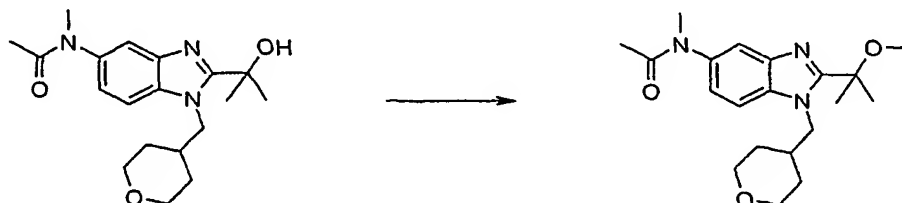
Step B. *N*-[2-(1-hydroxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide



Following the procedure for the step B in Example 112, using *N*-[3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl]-*N*-methylacetamide (1.14 g, 4.11 mmol) (for preparation, see the steps B, C and D in Example 103), 2-hydroxy-2-methylpropanoic acid (0.470 g, 4.52 mmol), diisopropylethylamine (0.800 g, 6.17 mmol) and HATU (1.88 g, 4.93 mmol) in DMF (40 mL) and then in acetic acid (50 mL), the crude product was purified by MPLC using EtOAc/MeOH (20:1) on silica

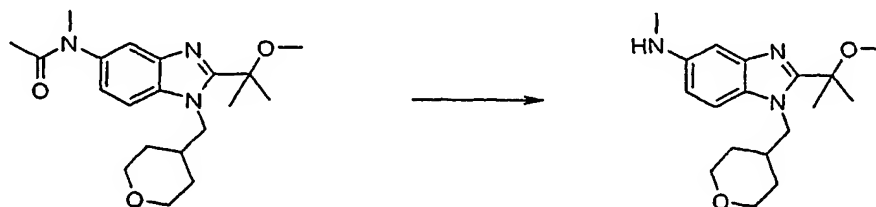
gel to give 0.475 g (33%) of a brown solid as the title compound. MS (ESI) (M+H)⁺: 346.03.

Step C. *N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide



Following the procedure for the step C in Example 112, using *N*-[2-(1-hydroxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide (103.1, 0.299 mmol), iodomethane (93.6 mg, 0.66 mmol) and sodium hydride (26.4 mg, 60%, 0.66 mmol) in THF (10 mL, 110 mg 100%) of the title compound was obtained as a colorless syrup. MS (ESI) (M+H)⁺: 360.05.

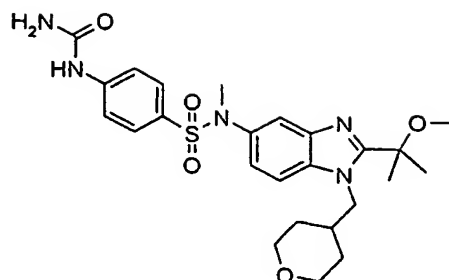
Step D. 2-(1-methoxy-1-methylethyl)-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine



Following the procedure for the step D in Example 112, using *N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide (110 mg, 0.299 mmol) in 5 mL of EtOH-2*N* HCl (3:2), 121.6 mg (100%) of a grey white solid was obtained as the title product. MS (ESI) (M+H)⁺: 318.57.

Example 121.

4-[(aminocarbonyl)amino]-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide

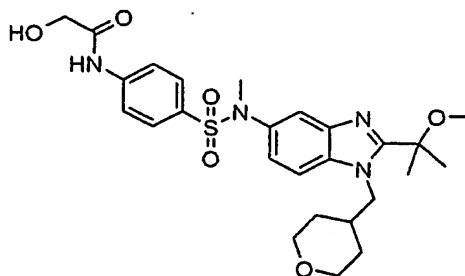


Following the procedure for the step A in Example 120, using 2-(1-methoxy-1-methylethyl)-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (48.6 mg, 0.120 mmol) (for preparation, see the steps B, C and
 5 D in example 120), DMAP (58.6 mg, 0.48 mmol) and 4-[(aminocarbonyl)amino]benzenesulfonyl chloride (42.1 mg, 0.178 mmol) in MeCN (5 mL), the crude product was purified by reversed-phase HPLC using 10-45% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 34.7 mg (56%); ¹HNMR (400 MHz, CD₃OD): δ 1.47 - 1.59 (m, 4
 10 H), 1.80 (s, 6 H), 2.31 - 2.46 (m, 1 H), 3.24 (s, 3 H), 3.34 (s, 3 H), 3.35 - 3.41 (m, 2 H), 3.87 - 4.04 (m, 2 H), 4.53 (d, J=7.42 Hz, 2 H), 7.28 (dd, J=8.79, 1.95 Hz, 1 H), 7.37 - 7.44 (m, 2 H), 7.47 (d, J=1.56 Hz, 1 H), 7.50 - 7.58 (m, 2 H), 7.81 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 516.0; Anal. Calcd for C₂₅H₃₃N₅O₅S+ 1.3TFA(663.87): C, 49.94, H, 5.21, N, 10.55; Found: C, 50.07; H, 5.16; N, 10.44.

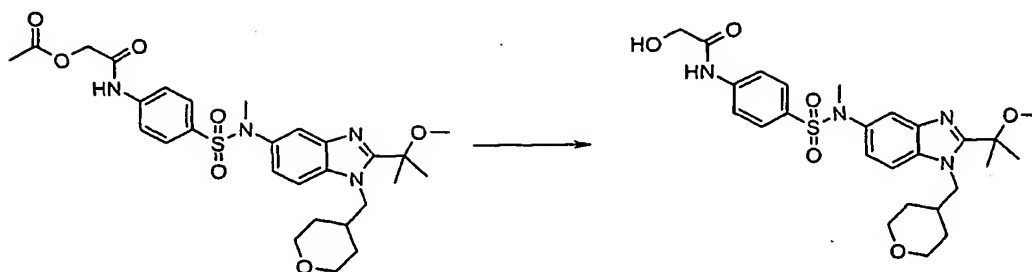
15

Example 122

2-Hydroxy-*N*-(4-{[[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methylamino)sulfonyl}phenyl)acetamide

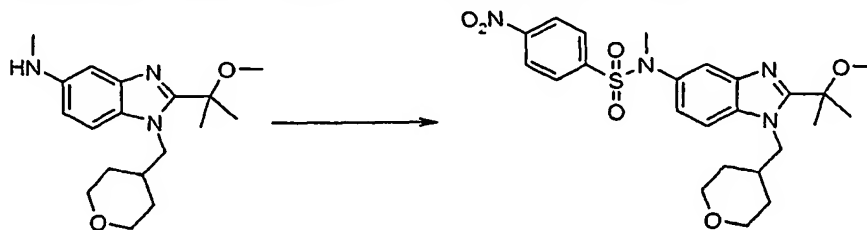


20 **Step A. 2-Hydroxy-*N*-(4-{[[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methylamino)sulfonyl}phenyl)acetamide**



Following the procedure for Example 110, using 2-[(4-[[[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)amino]-2-oxoethyl acetate (100 mg, crude, 0.097 mmol) (for preparation, see the following steps B, C and D) and a drop of sodium methoxide (25% in MeOH) in MeOH (10 mL), the crude product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 16.7 mg (32%); ¹HNMR (400 MHz, CD₃OD): δ 1.47 - 1.60 (m, 4 H), 1.80 (s, 6 H), 2.29 - 2.46 (m, 1 H), 3.25 (s, 3 H), 3.34 (s, 3 H), 3.35 - 3.40 (m, 2 H), 3.90 - 4.01 (m, 2 H), 4.13 (s, 2 H), 4.53 (d, J=7.42 Hz, 2 H), 7.27 (dd, J=8.88, 2.05 Hz, 1 H), 7.47 (d, J=2.15 Hz, 1 H), 7.48 - 7.53 (m, 2 H), 7.79 (s, 1 H), 7.79 - 7.84 (m, 2 H); MS (ESI) (M+H)⁺: 531.0; Anal. Calcd for C₂₆H₃₄N₄O₆S+ 1.40 TFA+0.2 H₂O (693.88): C, 49.85, H, 5.20, N, 8.07; Found: C, 49.78; H, 5.18; N, 8.20.

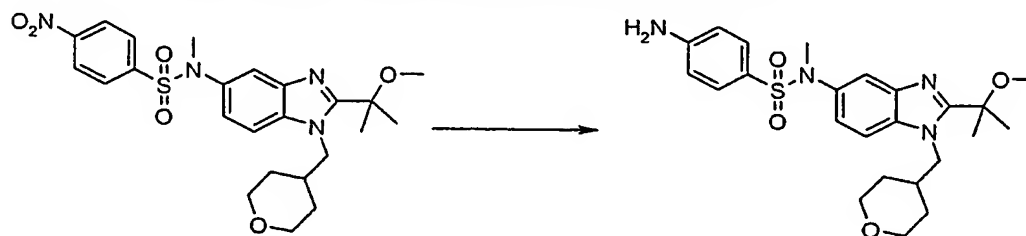
Step B. *N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-*N*-methyl-4-nitrobenzenesulfonamide



Following the procedure as in Example 104, using 2-(1-methoxy-1-methylethyl)-*N*-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine hydrochloride (72.9 mg, 0.179 mmol) (for preparation, see the steps B, C and D in example 62), DMAP (87.5 mg, 0.716 mmol) and 4-nitrobenzenesulfonyl chloride (59.8 mg, 0.269

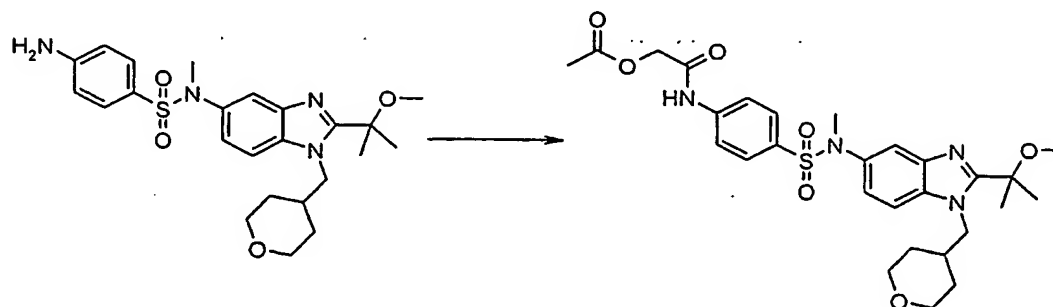
mmol) in MeCN (6 mL), the crude product was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 49.8 mg (55%) of a yellow solid as the title compound. MS (ESI) (M+H)⁺: 502.98.

5 **Step C. 4-Amino-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide**



Following the procedure for the step A in Example 107, using *N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-nitrobenzenesulfonamide (48.9 mg, 0.097 mmol) and 10% Pd/C (20 mg) in ethyl acetate (20 mL), 70.1 mg (100%) of a grey solid was obtained. MS (ESI) (M+H)⁺: 474.06.

15 **Step D. 2-[(4-[[[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl]phenyl)amino]-2-oxoethyl acetate**

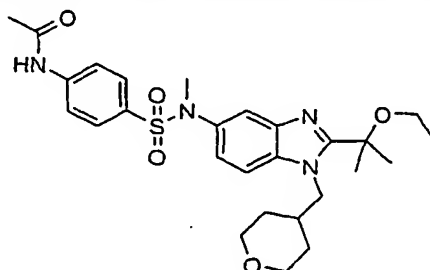


20 Following the procedure for Example 108, using 4-amino-*N*-[2-(1-methoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (70.1 mg, 0.097 mmol), DMAP (35.6 mg, 0.291 mmol)

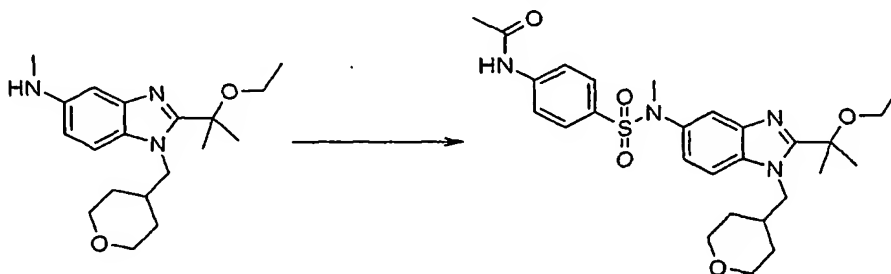
and 2-chloro-2-oxoethyl acetate (26.5 mg, 0.194mmol) in MeCN (6 mL), 100 mg of the crude title product was obtained, which was used directly for next step.

Example 123

- 5 *N*-(4-{[[2-(1-ethoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide



Step A. *N*-(4-{[[2-(1-ethoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide

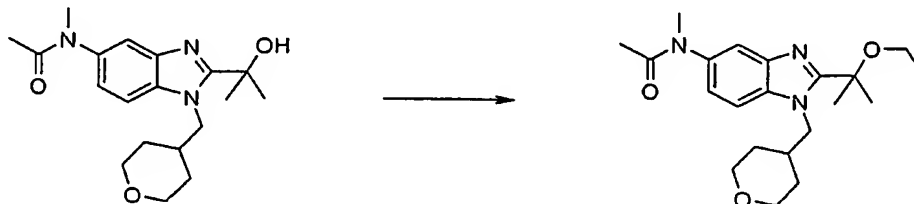


10

- Following the procedure as in Example 104, using 2-(1-ethoxy-1-methylethyl)-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (96.2 mg, 0.15 mmol) (for preparation, see the following steps B and C), DMAP (73.3 mg, 0.60 mmol) and 4-(acetylamino)benzenesulfonyl chloride (70.0 mg, 0.30 mmol) in MeCN (10 mL), the crude product was purified MPLC using EtOAc/MeOH (20:1) on silica gel to give 46.2 mg (55%) of a white solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 1.25 - 1.33 (m, 3 H), 1.43 - 1.64 (m, 4 H), 1.84 (s, 6 H), 2.14 (s, 3 H), 2.35 - 2.51 (m, 1 H), 3.25 (s, 3 H), 3.31 - 3.41 (m, 2 H), 3.60 (q, J=6.90 Hz, 2 H), 3.95 (m, 2 H), 4.62 (d, J=7.62 Hz, 2 H), 7.31 (dd, J=8.98, 2.15 Hz, 1 H), 7.43 - 7.50 (m, 2 H), 7.52 (d, J=1.76 Hz, 1 H), 7.67 - 7.76 (m, 2 H), 7.87 (d, J=8.79 Hz, 1 H); MS (ESI) (M+H)⁺: 529.0; Anal. Calcd for C₂₇H₃₆N₄O₅S + 0.7 HCl ++0.7
- 15
- 20

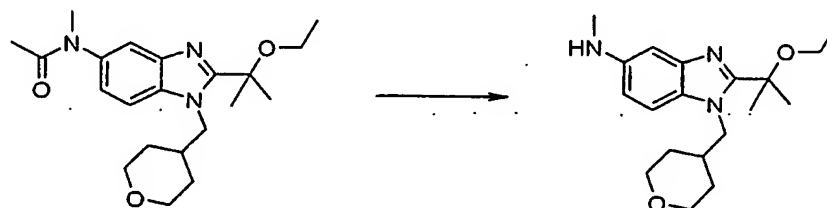
H₂O+0.6 CH₃OH (586.03): C, 56.57, H, 6.97, N, 9.56; Found: C, 56.60; H, 6.96; N, 9.59.

Step B. *N*-[2-(1-ethoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide



Following the procedure for step C in Example 120, using of *N*-[2-(1-hydroxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide (51.8 mg, 0.15 mmol) (for preparation see the step B in Example 120), sodium hydride (13.5 mg, 60%, 0.33 mmol) and iodoethane (51.5 mg, 0.33 mmol) in THF (5 mL), 73.5 mg (100%) of the title compound was obtained as a colorless syrup. MS (ESI) (M+H)⁺: 374.04.

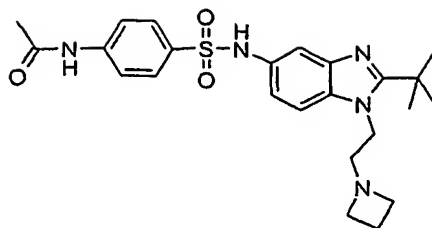
Step C. 2-(1-ethoxy-1-methylethyl)-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine



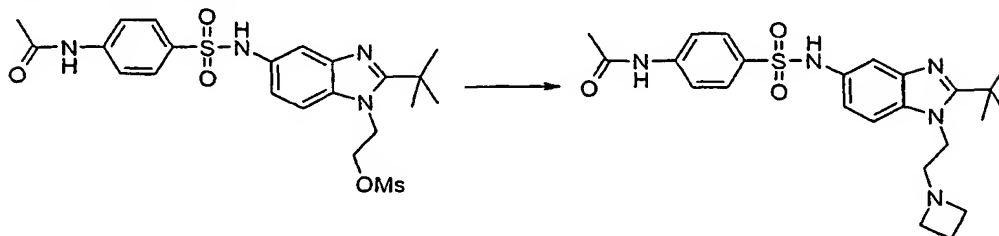
Following the procedure for step D in Example 120, using *N*-[2-(1-ethoxy-1-methylethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide of (73.5 mg, 0.15 mmol) in 5 mL of EtOH-2*N* HCl (3:2), 96.32 mg (100%) of a grey solid was obtained as the title product. MS (ESI) (M+H)⁺: 332.02.

Example 124

N-[4-([1-(2-azetidin-1-ylethyl)-2-*tert*-butyl-1*H*-benzimidazol-5-yl]amino)sulfonyl]phenyl]acetamide



Step A. *N*-[4-({[1-(2-azetidin-1-ylethyl)-2-*tert*-butyl-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]acetamide

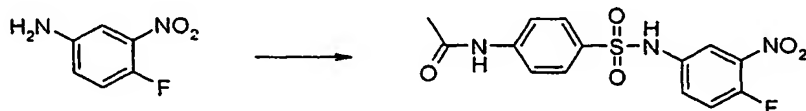


5

2-[5-({[4-(acetamidophenyl)sulfonyl]amino}-2-*tert*-butyl-1*H*-benzimidazol-1-yl)ethyl] methanesulfonate (0.10 g, 0.196 mmol), azetidine (0.20 g, 3.93 mmol) and KI (0.65 g, 0.393 mmol) were mixed together and heated to 80°C in DMF (3 mL). The solvent was concentrated. The crude product was purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and then lyophilized to give the title compound as the corresponding TFA salt. Yield: 30 mg (26%); MS (ESI) (M+H)⁺: 470.0.

10

Step B. *N*-(4-{{[4-fluoro-3-nitrophenyl]amino}sulfonyl}phenyl)acetamide

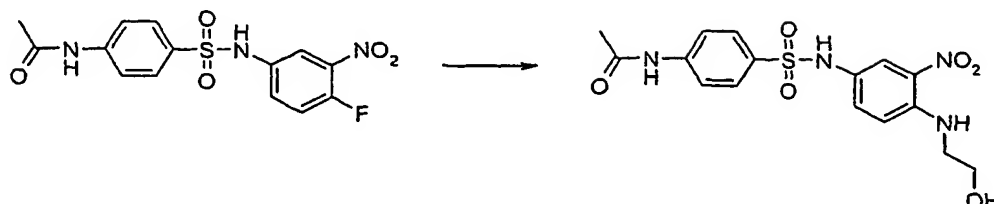


15

4-Fluoro-3-nitroaniline (6.22 g, 39.8 mmol) and 4-(acetamidophenyl)benzenesulfonyl chloride (10.2 g, 43.8 mmol) were heated to 50°C for 20hrs. in pyridine (70 mL). The solvent was concentrated. The crude product was recovered in DCM and washed with water, 2N HCl, saturated NaHCO₃ solution, water and brine. The organic layer was dried over anhydrous MgSO₄. The solvent was concentrated giving the title compound that was used for the next step without further purification. Yield: 10 g (70%); MS (ESI) (M+H)⁺: 354.0.

20

Step C. *N*-{4-[(4-[(2-hydroxyethyl)amino]-3-nitrophenyl)amino)sulfonyl]phenyl}acetamide

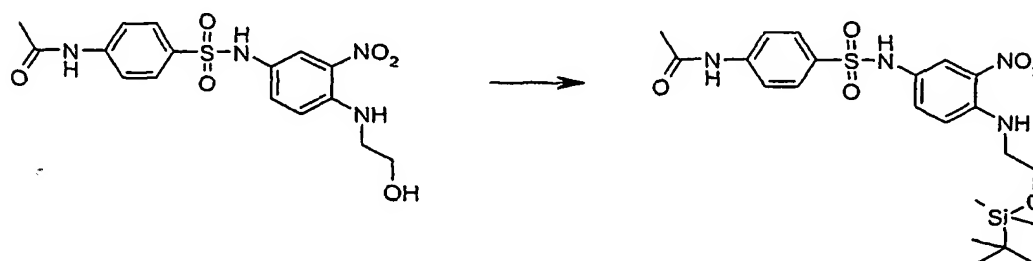


5

N-(4-[(4-[(2-hydroxyethyl)amino]-3-nitrophenyl)amino)sulfonyl]phenyl)acetamide (2.91 g, 8.23 mmol), 2-aminoethanol (3.00 mL, 49.4 mmol) and pyridine (1.33 mL, 16.4 mmol) in DMSO (30 mL) were heated at 90°C for 40 min. Cooled down to room temperature, the reaction mixture was poured into water (250 mL) at 0°C. The dark-purple mixture was acidified with concentrated HCl until red color appears. The compound was extracted with EtOAc (3X). The combined organic layers were washed with brine and dried over anhydrous MgSO₄. The solvent was concentrated giving the title compound that was used for the next step without further purification. Yield: 3.25 g (99%); MS (ESI) (M+H)⁺: 395.2.

15

Step D. *N*-{4-[(4-[(2-[(*tert*-butyl(dimethyl)silyl)oxy]ethyl)amino]-3-nitrophenyl)amino)sulfonyl]phenyl}acetamide

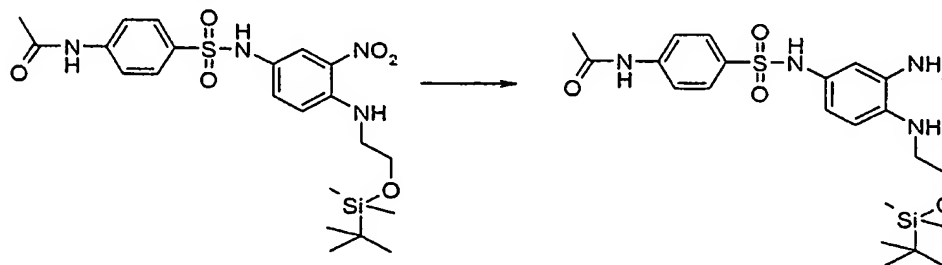


20 A solution of TBDMSCl (1.36g, 9.05 mmol) in EtOAc (100 mL) was slowly added to a solution of *N*-{4-[(4-[(2-hydroxyethyl)amino]-3-nitrophenyl)amino)sulfonyl]phenyl}acetamide (3.25 g, 8.23 mmol) and imidazole (0.67 g, 9.88 mmol) in EtOAc (250 mL) at room temperature. The reaction mixture was stirred overnight. The reaction was quenched with water and washed with

saturated NH_4Cl solution, water and brine. The organic layer was dried over anhydrous MgSO_4 . The solvent was concentrated. The crude product was purified by flash chromatography on silica gel using EtOAc/Hex (3:1) as eluent to give the title compound. Yield: 3.39 g (81%); MS (ESI) $(\text{M}+\text{H})^+$: 509.1.

5

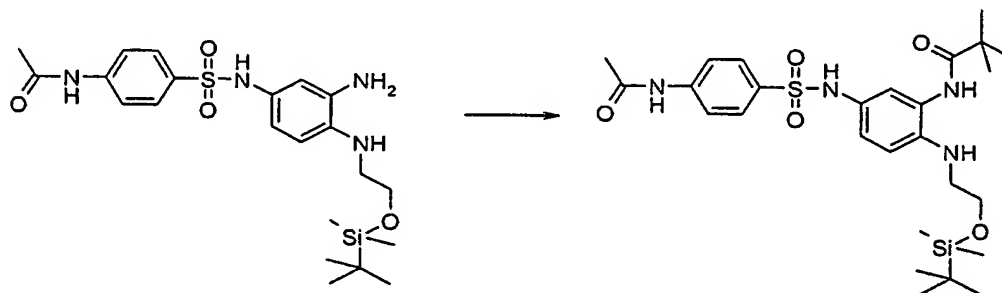
Step E. *N*-{4-[(3-amino-4-[(2-{*tert*-butyl(dimethyl)silyl)oxy]ethyl)amino]phenyl]amino)sulfonyl]phenyl}acetamide



N-{4-[(3-amino-4-[(2-{*tert*-butyl(dimethyl)silyl)oxy]ethyl)amino]-3-nitrophenyl]amino)sulfonyl]phenyl}acetamide (3.27 g, 6.42 mmol) was hydrogenated in EtOAc (200 mL) catalyzed by 10% Pd/C at 50 psi H_2 in Parr shaker overnight at room temperature. The mixture was filtered through a celite pad. The solvent was concentrated giving the title compound that was used for the next step without further purification. Yield: 3.05 g (99%); MS (ESI) $(\text{M}+\text{H})^+$: 479.1.

15

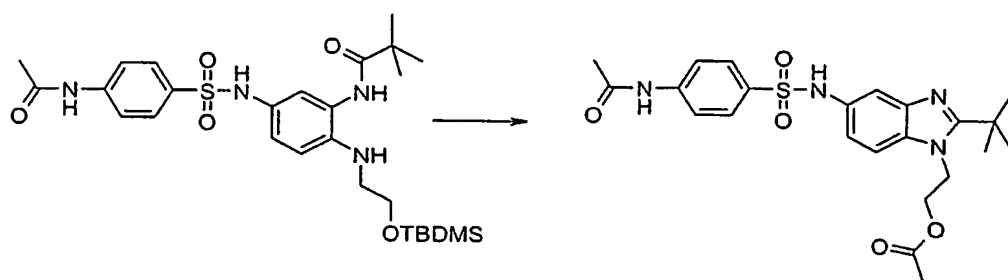
Step F. *N*-{5-[(4-(acetlamino)phenyl)sulfonyl]amino)-2-[(2-{*tert*-butyl(dimethyl)silyl)oxy]ethyl)amino]phenyl}-2,2-dimethylpropanamide



A solution of tBuCOCl (0.85 mL, 7.20 mmol) in DCM (50 mL) was added dropwise to a solution of *N*-{4-[(3-amino-4-[(2-{*tert*-butyl(dimethyl)silyl)oxy]ethyl)amino]phenyl]amino)sulfonyl]phenyl}acetamide

(3.05 g, 6.37 mmol) and Et₃N (1.20 mL, 8.60 mmol) in DCM (250 mL) at 0°C. The reaction mixture was stirred for 1.5 hours and washed with water (3X), saturated NaHCO₃ solution, water and brine. The organic layer was dried over anhydrous MgSO₄. The solvent was concentrated giving the title compound that was used for the
 5 next step without further purification. Yield: 3.59 g (99%); MS (ESI) (M+H)⁺: 563.0.

Step G. 2-[5-({[4-(acetylamino)phenyl]sulfonyl}amino)-2-*tert*-butyl-1*H*-benzimidazol-1-yl]ethyl acetate

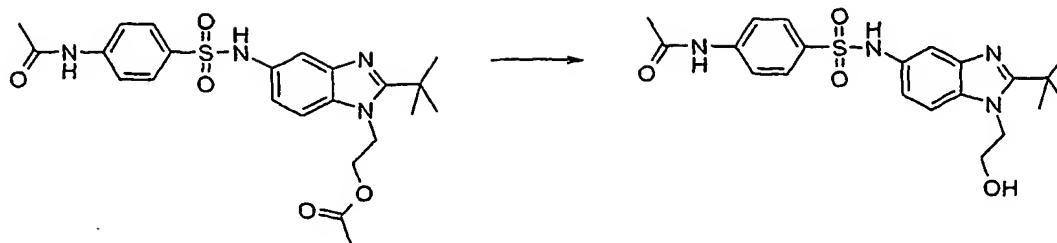


10

N-{5-({[4-(acetylamino)phenyl]sulfonyl}amino)-2-[(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino]phenyl}-2,2-dimethylpropanamide (2.87g, 5.10 mmol) was dissolved in glacial acetic acid (40 mL) heated to 170°C in a microwave oven for 15 min. The solvent was concentrated. The crude compound was purified on silica gel by
 15 flash chromatography using EtOAc as eluent. The fractions containing the desired material were purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and then lyophilized to give the title compound as the corresponding TFA salt. Yield: 260 mg (8%); ¹H NMR (400 MHz, CD₃OD): δ 1.64 (s, 9 H), 1.83 (s, 3 H), 2.10 (s, 3 H), 4.53 (t, J=5.66 Hz, 2 H), 4.83 - 4.90 (m, 2 H),
 20 7.27 (dd, J=9.08, 2.05 Hz, 1 H), 7.60 (d, J=1.95 Hz, 1 H), 7.62 - 7.73 (m, 4 H), 7.79 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 473.0; Anal. Calcd. for C₂₃H₂₈N₄O₅S + 1.30 TFA: C, 49.53; H, 4.76; N, 9.02. Found: C, 49.51; H, 4.43; N, 9.10.

Step H. *N*-[4-({[2-*tert*-butyl-1-(2-hydroxyethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]acetamide

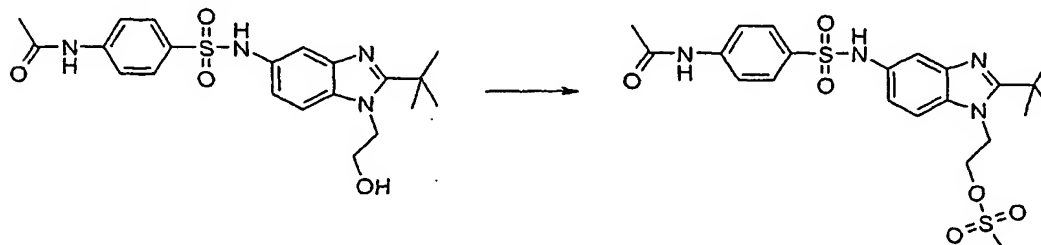
25



To 2-[5-({[4-(acetylamino)phenyl]sulfonyl}amino)-2-*tert*-butyl-1*H*-benzimidazol-1-yl]ethyl acetate (0.20 g, 0.423 mmol) in water (50 mL) was added 2N NaOH (5 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 2 hrs. The reaction mixture was neutralized with concentrated HCl at 0°C until precipitation occurs. The product was extracted with EtOAc (3X). The combined organic layers were dried over anhydrous Na₂SO₄ and filtered. The solvent was concentrated giving the pure title compound. Yield: 184 mg (99%), MS (ESI) (M+H)⁺: 431.0.

10

Step I. 2-[5-({[4-(acetylamino)phenyl]sulfonyl}amino)-2-*tert*-butyl-1*H*-benzimidazol-1-yl]ethyl methanesulfonate

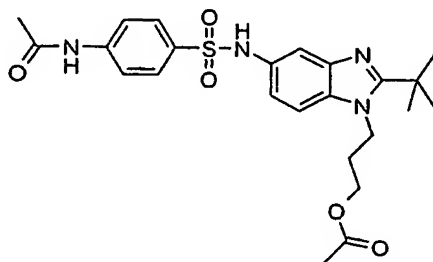


Methane sulfonyl chloride (0.36 mL, 0.47 mmol) was added to a solution of *N*-[4-({[2-*tert*-butyl-1-(2-hydroxyethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]acetamide (0.18 g, 0.42 mmol) and Et₃N (0.90 mL, 0.64 mmol) in a 1:1 mixture of EtOAc:DCM (120 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 3 hrs. The solvent was concentrated and the crude product was recovered in EtOAc (150 mL). The organic phase was washed with water, saturated NaHCO₃ solution, water and brine. The solution was dried over anhydrous MgSO₄ and filtered. The solvent was concentrated giving the pure title compound. Yield: 205 mg (94%); MS (ESI) (M+H)⁺: 509.1.

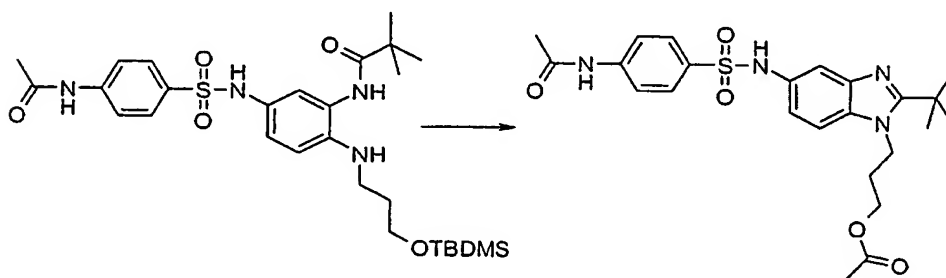
20

Example 125

3-[5-([4-(acetylamino)phenyl]sulfonyl)amino]-2-*tert*-butyl-1*H*-benzimidazol-1-yl]propyl acetate

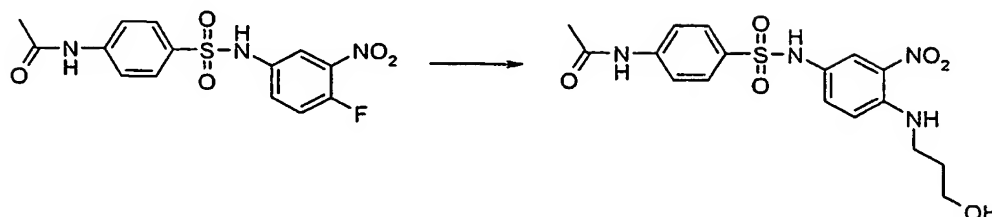


5 Step A. 3-[5-([4-(acetylamino)phenyl]sulfonyl)amino]-2-*tert*-butyl-1*H*-benzimidazol-1-yl]propyl acetate



N-{5-([4-(acetylamino)phenyl]sulfonyl)amino)-2-[(3-{*tert*-butyl(dimethyl)silyl}oxy)propyl]amino]phenyl)-2,2-dimethylpropanamide (2.56 g, 4.44 mmol) (for preparation, see Example 124, Steps B to F) was dissolved in acetic acid (150 mL) and heated to 80°C overnight. The solvent was concentrated. The residue was recovered in EtOAc and washed with saturated NaHCO₃ solution, water and brine. The organic layer was dried with anhydrous MgSO₄, filtered and concentrated. The crude compound was purified on silica gel by flash chromatography using MeOH 1% to 5% in EtOAc as eluent. The fractions containing the desired material were purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and then lyophilized to give the title compound as the corresponding TFA salt. Yield: 60 mg (2%); ¹H NMR (400 MHz, CD₃OD): δ 1.63 (s, 9 H), 2.04 (s, 3 H), 2.10 (s, 3 H), 2.20 - 2.31 (m, 2 H), 4.25 (t, J=5.86 Hz, 2 H), 4.59 - 4.69 (m, 2 H), 7.28 (dd, J=8.88, 2.05 Hz, 1 H), 7.58 - 7.67 (m, 3 H), 7.67 - 7.75 (m, 3 H); MS (ESI) (M+H)⁺: 487.0; Anal. Calcd. for C₂₄H₃₀N₄O₅S + 1.30 TFA: C, 50.33; H, 4.97; N, 8.83. Found: C, 50.42; H, 5.10; N, 8.66.

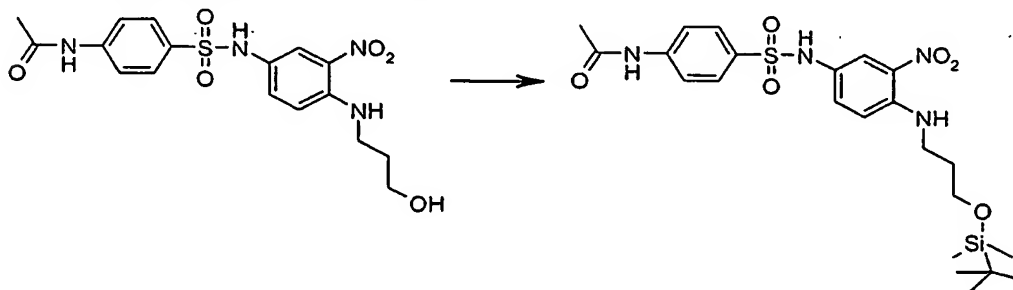
Step B. *N*-{4-[(4-[(3-hydroxypropyl)amino]-3-nitrophenyl)amino)sulfonyl]phenyl}acetamide



5 *N*-(4-[(4-[(3-hydroxypropyl)amino]-3-nitrophenyl)amino)sulfonyl]phenyl)acetamide (4.00 g, 11.3 mmol) (for preparation, see Example 124, Step B), 3-aminopropanol (4.25 g, 56.6 mmol) and pyridine (1.83 mL, 22.6 mmol) in DMSO (50 mL) were heated to 80°C overnight. The room temperature cooled down reaction mixture was poured in water (400 mL) at 0°C. The dark-purple mixture was acidified with concentrated HCl until
 10 red color appears. The compound was extracted with EtOAc (3X). The combined organic layers were washed with brine and dried over anhydrous MgSO₄. The solvent was concentrated. The crude product was purified by flash chromatography on silica gel, using EtOAc as eluent, giving the title compound. Yield: 1.67 g (36%); MS (ESI) (M+H)⁺: 409.4.

15

Step C. *N*-{4-[(4-[(3-{[*tert*-butyl(dimethyl)silyl]oxy}propyl)amino]-3-nitrophenyl)amino)sulfonyl]phenyl}acetamide

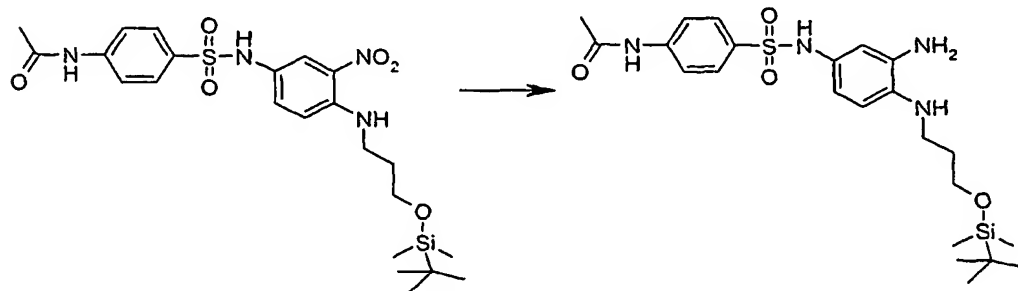


A solution of TBDMSCl (0.74 g, 4.90 mmol) in EtOAc (50 mL) was slowly added to
 20 a solution of *N*-{4-[(4-[(3-hydroxypropyl)amino]-3-nitrophenyl)amino)sulfonyl]phenyl}acetamide (1.67 g, 4.08 mmol) and imidazole (0.36 g, 5.31 mmol) in EtOAc (200 mL) at room temperature. The reaction mixture was stirred overnight. The reaction was quenched with water and washed with NH₄Cl

saturated solution, water and brine. The organic layer was dried over anhydrous MgSO_4 . The solvent was concentrated. The crude product was purified by flash chromatography on silica gel, using EtOAc/Hex (3:1) as eluent, giving the title compound. Yield: 2.06 g (99%); MS (ESI) $(\text{M}+\text{H})^+$: 523.8.

5

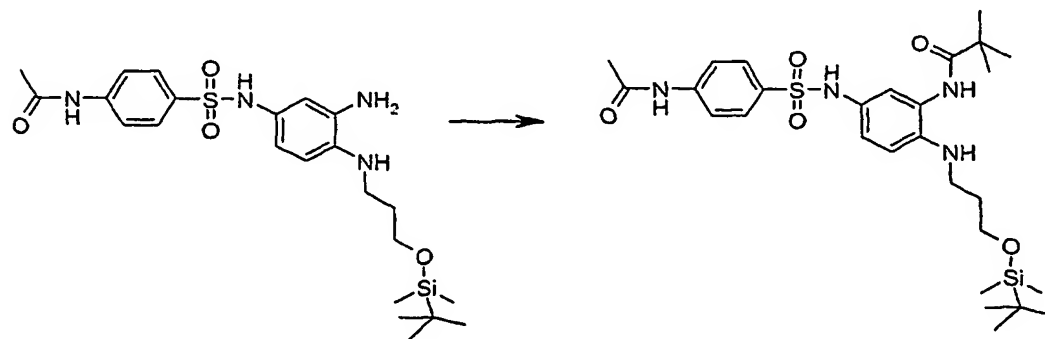
Step E. *N*-{4-[[[3-amino-4-[(3-[[*tert*-butyl(dimethyl)silyl]oxy]propyl)amino]phenyl]amino)sulfonyl]phenyl}acetamide



N-{4-[[[4-[(3-[[*tert*-butyl(dimethyl)silyl]oxy]propyl)amino]-3-nitrophenyl]amino)sulfonyl]phenyl}acetamide (2.06 g, 3.94 mmol) was hydrogenated in EtOAc (200 mL) catalyzed by 10% Pd/C at 50 psi H_2 in Parr shaker overnight at room temperature. The mixture was filtered over a celite pad. The solvent was concentrated giving the title compound that was used for the next step without further purification. Yield: 1.78 g (91%); MS (ESI) $(\text{M}+\text{H})^+$: 493.6.

15

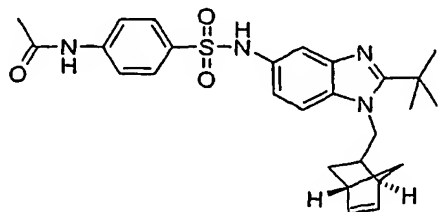
Step F. *N*-{5-[[[4-(acetamino)phenyl]sulfonyl]amino]-2-[(3-[[*tert*-butyl(dimethyl)silyl]oxy]propyl)amino]phenyl}-2,2-dimethylpropanamide



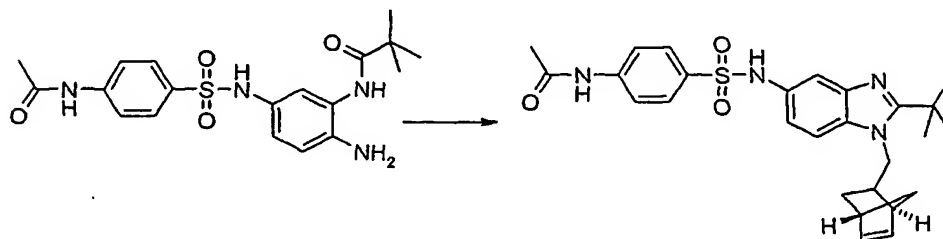
- tBuCOCl (0.44 mL, 3.61 mmol) was added to a solution of *N*-{4-[(3-amino-4-[(3-
 {{*tert*-butyl(dimethyl)silyl}oxy}propyl)amino]phenyl]amino)sulfonyl]phenyl}
 acetamide (1.78 g, 3.61 mmol) and Et₃N in DCM at 0°C. The reaction mixture was
 stirred for 3hrs. at 0°C. The reaction was quenched with saturated NaHCO₃ solution.
 5 The organic layer was washed with water, brine and dried over anhydrous MgSO₄.
 The solvent was concentrated giving the title compound that was used for the next
 step without further purification. Yield: 2.06 g (98%); MS (ESI) (M+H)⁺: 577.9.

Example 126

- 10 *N*-{4-[(1-[(1*S*,4*S*)-bicyclo[2.2.1]hept-5-en-2-ylmethyl]-2-*tert*-butyl-1*H*-
 benzimidazol-5-yl]amino)sulfonyl]phenyl}acetamide



StepA. *N*-{4-[(1-[(1*S*,4*S*)-bicyclo[2.2.1]hept-5-en-2-ylmethyl]-2-*tert*-butyl-1*H*-
 benzimidazol-5-yl]amino)sulfonyl]phenyl}acetamide



- 15 *N*-[5-([4-(acetylamino)phenyl]sulfonyl)amino]-2-amino phenyl]-2,2-dimethyl
 propanamide (200 mg, 0.494 mmol) (for preparation, see the following steps B to D)
 and (1*S*, 4*S*)-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (60 mg, 0.494 mmol) were
 mixed together in acetic acid (15 mL). The reaction mixture was heated to 50°C and
 stirred for 1 hr. Na(BH₃)CN (31 mg, 0.494 mmol) was added to the warm solution
 20 and stirred for one extra hour (50°C). The reaction mixture was heated to 100°C for 3
 days (typically overnight). The solvent was concentrated. The crude product was
 purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and
 then lyophilized to give the title compound as the corresponding TFA salt. Yield: 30

mg (10%); ^1H NMR (400 MHz, CD_3OD): δ 0.80 - 0.90 (m, 1 H), 1.26 - 1.36 (m, 1 H), 1.37 - 1.45 (m, 1 H), 1.45 - 1.53 (m, 1 H), 1.63 (d, $J=6.83$ Hz, 9 H), 1.79 - 1.90 (m, 1 H), 2.10 (s, 3 H), 2.11 - 2.20 (m, 1 H), 2.57 (s, 1 H), 2.85 (s, 1 H), 2.93 (s, 1 H), 4.13 - 4.44 (m, 1 H), 4.45 - 4.73 (m, 1 H), 5.91 - 6.15 (m, 1 H), 6.24 - 6.46 (m, 1 H), 7.26 (td, $J=8.98, 2.15$ Hz, 1 H), 7.62 (dd, $J=4.78, 2.05$ Hz, 1 H), 7.63 - 7.76 (m, 5 H); MS (ESI) ($\text{M}+\text{H}$) $^+$: 493.0; Anal. Calcd. for $\text{C}_{27}\text{H}_{32}\text{N}_4\text{O}_3\text{S} + 1.70 \text{ TFA} + 1.00 \text{ H}_2\text{O} + 0.50 \text{ MeCN}$: C, 52.02; H, 5.17; N, 8.69. Found: C, 52.01; H, 5.13; N, 8.66.

Step B. *N*-(2-amino-5-nitrophenyl)-2,2-dimethylpropanamide



10

tBuCOCl (10.9 mL, 88.5 mmol) was added to a mixture of 2-amino-4-nitroaniline (13.5 g, 88.5 mmol) and pyridine (7.50 mL, 92.9 mmol) in DCM (600 mL) at 0°C . The reaction mixture was slowly allowed to warm to room temperature and stirred for 4hrs. The reaction mixture was washed with water, 0.1 N HCl, brine and dried over anhydrous MgSO_4 . The volume of the organic layer was reduced to 200 mL. The resulting precipitate was filtered off and washed with small amount of cold DCM. The operation was repeated 3 times, giving the title compound as a pale-yellow solid. Yield: 9.35 g (44%); MS (ESI) ($\text{M}+\text{H}$) $^+$: 238.2.

15

Step C. *N*-(2,5-diaminophenyl)-2,2-dimethylpropanamide

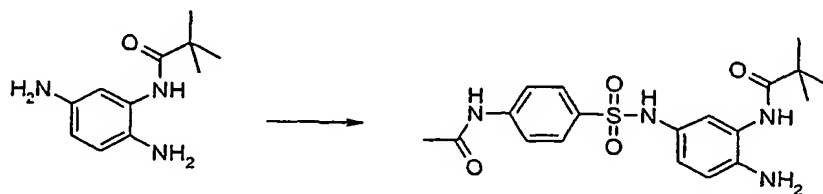


20

N-(2-amino-5-nitrophenyl)-2,2-dimethylpropanamide (9.35 g, 39.4 mmol) was hydrogenated in EtOAc (400 mL) catalyzed by 10% Pd/C at 40 psi H_2 in Parr shaker overnight at room temperature. The mixture was filtered through a celite pad. The solvent was concentrated giving the title compound that was used for the next step without further purification. Yield: 8.12 g (99%); MS (ESI) ($\text{M}+\text{H}$) $^+$: 208.2.

25

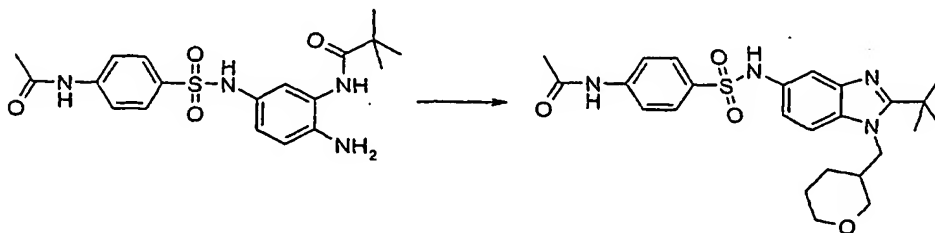
Step D. *N*-[5-([4-(acetylamino)phenyl]sulfonyl)amino]-2-aminophenyl]-2,2-dimethylpropanamide



- 5 4-(Acetylamino)benzenesulfonyl chloride (4.89 g, 20.9 mmol) was added by portion (over 3hrs) to a solution of *N*-(2,5-diaminophenyl)-2,2-dimethylpropanamide (4.34 g, 20.9 mmol) and pyridine (20 mL) in MeCN (600 mL). During the addition, the reaction temperature was maintained between -30 and -40°C. The reaction mixture was allowed to warm to room temperature and stirred for 1hr. The solvent was
- 10 concentrated. The residue was triturated in Et₂O and filtered. The resulting solid was stirred in water (200 mL), filtered and air-dried giving the title compound that was used for the next step without further purification. Yield: 6.2 g (73%); MS (ESI) (M+H)⁺: 405.1.

15 **Example 127**

N-[4-([2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-3-ylmethyl)-1*H*-benzimidazol-5-yl]amino)sulfonylphenyl]acetamide

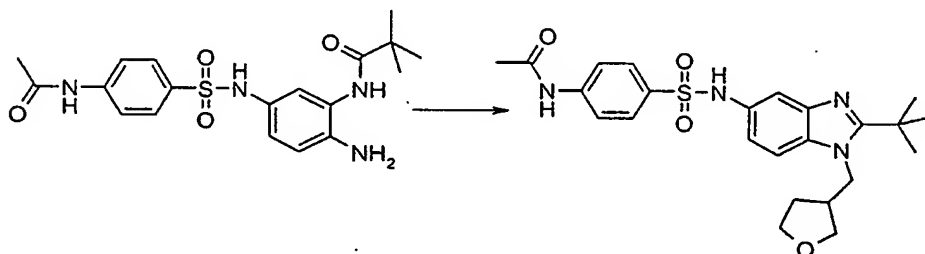


- 20 *N*-[5-([4-(acetylamino) phenyl] sulfonyl) amino) -2-amino phenyl] -2,2- dimethyl propanamide (73 mg, 0.18 mmol) (for preparation, see Example 126, Steps B to D) and tetrahydro-2*H*-pyran-3-carbaldehyde (31 mg, 0.27 mmol) were stirred together at room temperature for 1hr. in a 2:1 mixture of DCE and acetic acid (3 mL). Borane-pyridine complex (45 µL, 0.36 mmol) and concentrated HCl (5 drops) were added to the reaction mixture. The reaction mixture was heated to 95°C overnight. The solvent

was concentrated. The crude product was purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and then lyophilized to give the title compound as the corresponding TFA salt. Yield: 25 mg (23%); ¹H NMR (400 MHz, CD₃OD): δ 1.26 - 1.31 (m, 1 H), 1.50 - 1.61 (m, 1 H), 1.63 (s, 9 H), 1.67 - 1.77 (m, 2 H), 1.77 - 1.87 (m, 1 H), 2.10 (s, 3 H), 2.24 - 2.34 (m, 1 H), 3.39 (dd, J=11.62, 7.71 Hz, 1 H), 3.55 - 3.62 (m, 1 H), 3.66 (dd, J=11.52, 2.93 Hz, 1 H), 3.71 - 3.80 (m, 1 H), 4.38 (dd, J=15.04, 6.05 Hz, 1 H), 4.59 (dd, J=15.04, 8.98 Hz, 1 H), 7.24 (dd, J=8.98, 1.95 Hz, 1 H), 7.61 (d, J=2.15 Hz, 1 H), 7.63 - 7.68 (m, 2 H), 7.69 - 7.74 (m, 2 H), 7.76 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 485.0; Anal. Calcd. for C₂₅H₃₂N₄O₄S + 1.50 TFA: C, 51.29; H, 5.15; N, 8.55. Found: C, 51.43; H, 5.22; N, 8.11.

Example 128

N-[4-({[2-*tert*-butyl-1-(tetrahydrofuran-3-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]acetamide

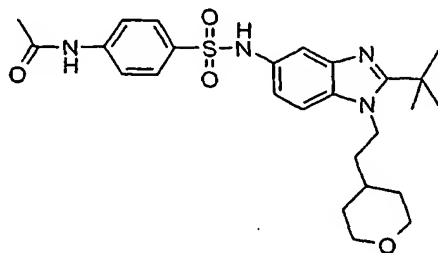


N-[5-({[4-(acetamino) phenyl] sulfonyl} amino) -2-amino phenyl] -2,2- dimethyl propanamide (113 mg, 0.27 mmol) (for preparation, see Example 126, Steps B to D), 50% tetrahydrofuran-3-carbaldehyde aqueous solution (60 mg, 0.27 mmol) and concentrated HCl (4 drops) were stirred together at room temperature in a 1:1 mixture of water and MeCN (15 mL). Borane-pyridine complex (69 µL, 0.55 mmol) was added and the reaction mixture was heated to 95°C overnight. The solvent was concentrated. The crude product was purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and then lyophilized to give the title compound as the corresponding TFA salt. Yield: 25 mg (15%); ¹H NMR (400 MHz, CD₃OD): δ 1.63 (s, 9 H), 1.74 - 1.85 (m, 1 H), 2.04 - 2.16 (m, 4 H), 2.98 (dd, J=7.91, 5.37 Hz, 1 H), 3.60 (d, J=5.47 Hz, 2 H), 3.68 - 3.78 (m, 1 H), 3.95 - 4.04 (m, 1 H), 4.53 (d, J=7.81 Hz, 2 H), 7.25 (dd, J=8.98, 2.15 Hz, 1 H), 7.59 - 7.68 (m, 3 H), 7.68 - 7.73 (m,

2 H), 7.76 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 471.0; Anal. Calcd. for C₂₄H₃₀N₄O₄S + 1.40 TFA + 0.10 H₂O + 0.10 MeCN: C, 50.98; H, 5.05; N, 9.03. Found: C, 51.01; H, 4.79; N, 9.01.

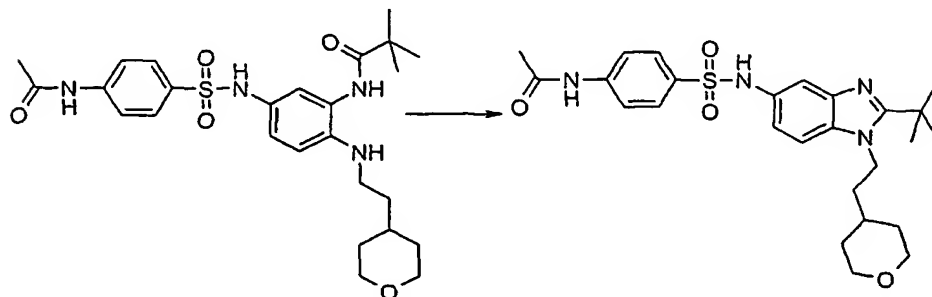
5 Example 129

N-{4-[(2-*tert*-butyl-1-[2-(tetrahydro-2*H*-pyran-4-yl)ethyl]-1*H*-benzimidazol-5-yl)amino)sulfonyl]phenyl}acetamide



Step A. *N*-{4-[(2-*tert*-butyl-1-[2-(tetrahydro-2*H*-pyran-4-yl)ethyl]-1*H*-benzimidazol-5-yl)amino)sulfonyl]phenyl}acetamide

10



N-(5-({[4-(acetylamino)phenyl]sulfonyl}amino)-2-([2-(tetrahydro-2*H*-pyran-4-yl)ethyl]amino)phenyl)-2,2-dimethylpropanamide (95 mg, 0.183 mmol) (for preparation, see the following step B) in acetic acid was heated to 100°C (10 mL)

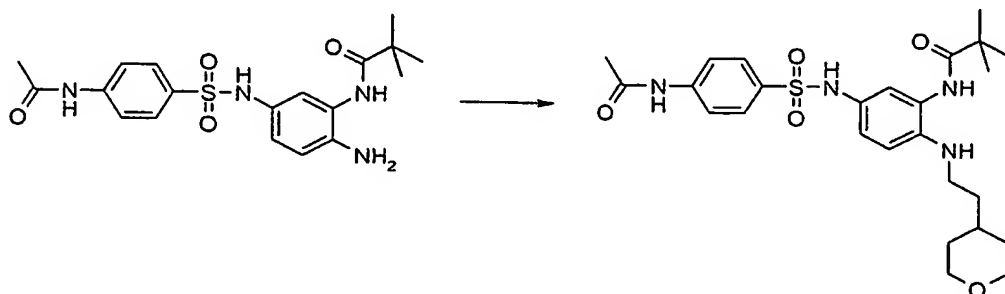
15 overnight. The solvent was concentrated. The crude product was purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and then lyophilized to give the title compound as the corresponding TFA salt. Yield: 50 mg (44%); ¹H NMR (400 MHz, CD₃OD): δ 1.32 - 1.48 (m, 1 H), 1.62 (s, 9 H), 1.75 (d, J=12.89 Hz, 2 H), 1.79 - 1.89 (m, 2 H), 2.10 (s, 3 H), 3.40 - 3.51 (m, 4 H), 3.95 (dd, J=11.81, 4.00 Hz, 2 H), 4.52 - 4.60 (m, 2 H), 7.28 (dd, J=8.98, 2.15 Hz, 1 H), 7.60 - 7.65 (m, 2 H), 7.65 - 7.68 (m, 2 H), 7.68 - 7.74 (m, 2 H); MS (ESI) (M+H)⁺: 499.0;

20

Anal. Calcd. for $C_{26}H_{34}N_4O_4S + 1.60 \text{ TFA} + 0.20 \text{ H}_2\text{O}$: C, 51.22; H, 5.30; N, 8.18.

Found: C, 51.29; H, 5.26; N, 8.13.

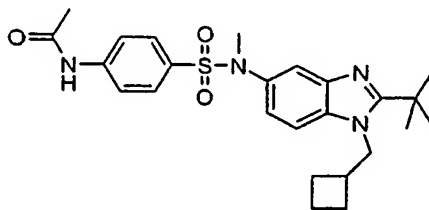
Step B. *N*-(5-([4-(acetylamino)phenyl]sulfonyl)amino)-2-([2-(tetrahydro-2*H*-pyran-4-yl)ethyl]amino)phenyl)-2,2-dimethylpropanamide



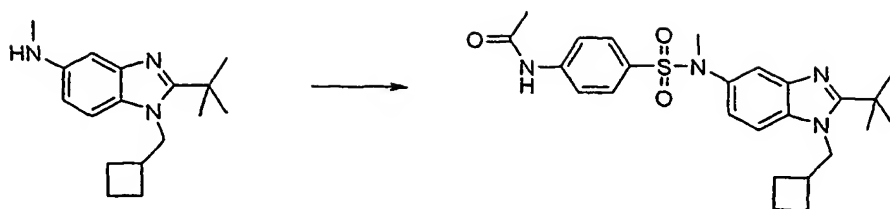
N-[5-([4-(acetylamino) phenyl] sulfonyl) amino) -2-amino phenyl] -2,2- dimethyl propanamide (90 mg, 0.22 mmol) (for preparation, see Example 126, steps B to D) and tetrahydro-2*H*-pyran-4-ylacetaldehyde (85 mg, 0.66 mmol) were stirred together in acetic acid (8 mL) at 70°C for 1 hr. The reaction mixture was cooled to room temperature and $\text{Na}(\text{BH})_3\text{CN}$ (30 mg, 0.44 mmol) was added. The reaction was stirred overnight at room temperature. The solvent was concentrated. The crude product was purified by preparative reverse-phase HPLC using 10-90% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ as eluent and then lyophilized to give the title compound as the corresponding TFA salt. Yield: 95 mg (69%); MS (ESI) ($\text{M}+\text{H}$)⁺: 517.6.

Example 130

N-(4-([2-*tert*-butyl-1-(cyclobutylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino)sulfonyl)phenyl)acetamide

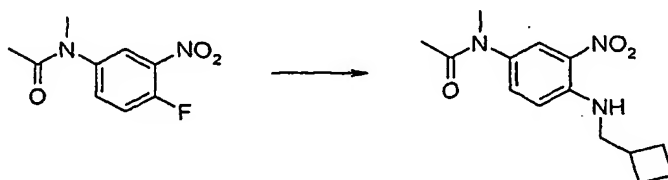


Step A. *N*-(4-([2-*tert*-butyl-1-(cyclobutylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino)sulfonyl)phenyl)acetamide



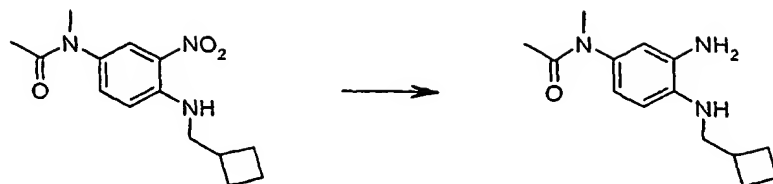
4-(acetylamino)benzenesulfonyl chloride (55 mg, 0.2 mmol) was added to a solution of 2-*tert*-butyl-1-(cyclobutylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (53 mg, 0.19 mmol) (for preparation, see Steps B to E) and DMAP (48 mg, 0.39 mmol) in MeCN (5 mL) at 70°C. The reaction mixture was stirred for 1 hr. and allowed to cool to room temperature. The solvent was concentrated. The crude product was purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and then lyophilized to give the title compound as the corresponding TFA salt. Yield: 82 mg (71%); ¹H NMR (400 MHz, CD₃OD): δ 1.65 (s, 9 H), 1.83 - 1.97 (m, 3 H), 2.04 - 2.13 (m, 3 H), 2.14 (s, 3 H), 2.79 - 2.93 (m, 1 H), 3.25 (s, 3 H), 4.64 (d, J=6.64 Hz, 2 H), 7.31 (dd, J=9.08, 2.05 Hz, 1 H), 7.41 - 7.49 (m, 2 H), 7.52 (d, J=1.95 Hz, 1 H), 7.71 (d, J=8.79 Hz, 2 H), 7.80 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 469.0.

15 **Step B . *N*-{4-[(cyclobutylmethyl)amino]-3-nitrophenyl}-*N*-methylacetamide**



A solution of (cyclobutylmethyl)amine in Et₂O (excess) was added to a solution of *N*-(4-fluoro-3-nitrophenyl)-*N*-methylacetamide (1.00 g, 4.71 mmol) and DIPEA (1.00 mL, 5.65 mmol) in DMF (50 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was concentrated. The crude product was purified by flash chromatography on silica gel, using EtOAc/Hep (30 to 90%) as eluent, giving the title compound. Yield: 1.01 g (77%); MS (ESI) (M+H)⁺: 278.3.

25 **Step C. *N*-{3-amino-4-[(cyclobutylmethyl)amino]phenyl}-*N*-methylacetamide**



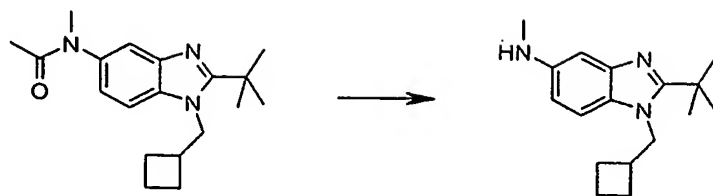
N-{4-[(cyclobutylmethyl)amino]-3-nitrophenyl}-*N*-methylacetamide (1.01 g, 3.64 mmol) was hydrogenated in EtOAc (150 mL) catalyzed by 10% Pd/C at 50 psi H₂ in Parr shaker overnight at room temperature. The mixture was filtered through a celite pad. The solvent was concentrated giving the title compound that was used for the next step without further purification. Yield: 833 mg (92%); MS (ESI) (M+H)⁺: 248.3.

Step D. *N*-[2-*tert*-butyl-1-(cyclobutylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide



*t*BuCOCl (0.41 mL, 3.36 mmol) was added to a solution of *N*-{3-amino-4-[(cyclobutylmethyl)amino]phenyl}-*N*-methylacetamide (0.83 mg, 3.36 mmol) and Et₃N (0.50 mL, 3.53 mmol) in DCM (125 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 3 hrs. The solvent was concentrated and the crude compound was recovered in acetic acid (100 mL). The solution was heated to 100°C overnight. The solvent was concentrated. The crude product was purified by flash chromatography on silica gel, using EtOAc/Hep (30 to 90%) as eluent, giving the title compound. Yield: 529 mg (50%); MS (ESI) (M+H)⁺: 314.4.

Step E. 2-*tert*-butyl-1-(cyclobutylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine

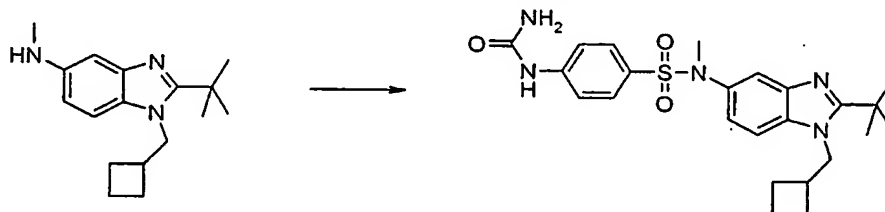


5 *N*-[2-*tert*-butyl-1-(cyclobutylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide (0.53 g, 1.68 mmol) was heated to 80°C overnight in concentrated HCl (10 mL). The room temperature cooled down reaction mixture was poured in water (100 mL). The resulting mixture was brought to slightly basic pH using NaOH solution at 0°C. The compound was extracted with EtOAc (3X) and the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and filtered. The solvent was concentrated giving the title compound that was used for the next step without further purification. Yield: 343 mg (75%); MS (ESI) (M+H)⁺: 272.4.

10

Example 131

4-[(aminocarbonyl)amino]-*N*-[2-*tert*-butyl-1-(cyclobutylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide

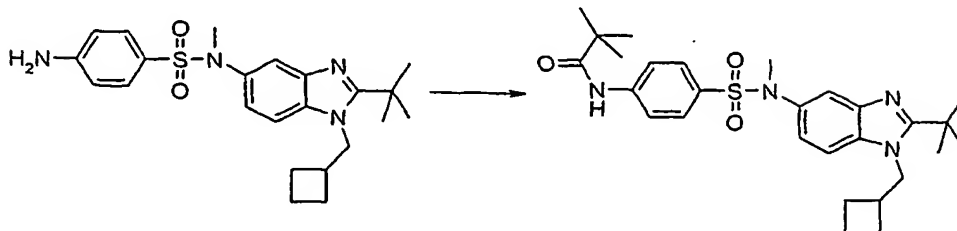


15 Following the procedure for Step A in Example 130, , using the 4-[(aminocarbonyl)amino] benzenesulfonyl chloride (57 mg, 0.24 mmol) and 2-*tert*-butyl-1-(cyclobutylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (55 mg, 0.20 mmol), the title compound was obtained as the corresponding TFA salt. Yield: 60 mg (50%); ¹H NMR (400 MHz, CD₃OD): δ 1.65 (s, 9 H), 1.81 - 1.99 (m, 3 H), 2.04 - 2.15 (m, 3 H), 2.80 - 2.92 (m, 1 H), 3.23 (s, 3 H), 4.64 (d, J=6.44 Hz, 2 H), 7.33 (dd, J=9.08, 2.05 Hz, 1 H), 7.36 - 7.42 (m, 2 H), 7.50 (d, J=1.95 Hz, 1 H), 7.51 - 7.56 (m, 2 H), 7.81 (d, J=9.18 Hz, 1 H); MS (ESI) (M+H)⁺: 470.0.

20

Example 132

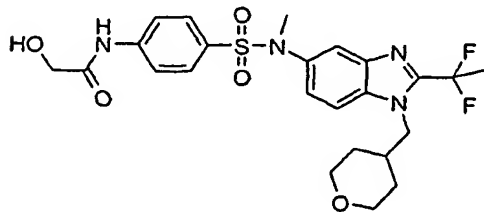
N-(4-([2-*tert*-butyl-1-(cyclobutylmethyl)-1*H*-benzimidazol-5-yl](methylamino)sulfonyl)phenyl)-2,2-dimethylpropanamide



- 5 2,2-Dimethylpropanoyl chloride (31 mg, 0.25 mol) was added to a solution of 4-amino-*N*-[2-*tert*-butyl-1-(cyclobutylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (100 mg, 0.23 mmol) and Et₃N (40 μ L, 0.28 mmol) in DCM (15 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. The solvent was concentrated. The crude product
- 10 was purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and then lyophilized to give the title compound as the corresponding TFA salt. Yield: 95 mg (64%); ¹H NMR (400 MHz, CD₃OD): δ 1.29 (s, 9 H), 1.65 (s, 9 H), 1.80 - 1.98 (m, 2 H), 2.04 - 2.15 (m, 4 H), 2.80 - 2.93 (m, 1 H), 3.25 (s, 3 H), 4.64 (d, *J*=6.44 Hz, 2 H), 7.31 (dd, *J*=8.98, 2.15 Hz, 1 H), 7.41 - 7.48 (m, 2 H), 7.51 (d, *J*=1.56 Hz, 1 H),
- 15 7.73 - 7.79 (m, 2 H), 7.81 (d, *J*=8.98 Hz, 1 H); MS (ESI) (*M*+*H*)⁺: 511.0.

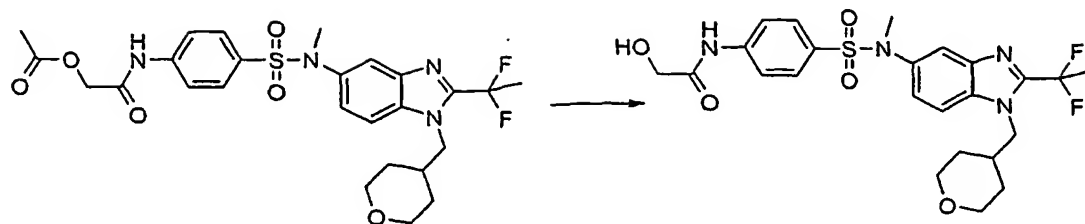
Example 133

N-(4-([2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methylamino)sulfonyl)phenyl)-2-hydroxyacetamide



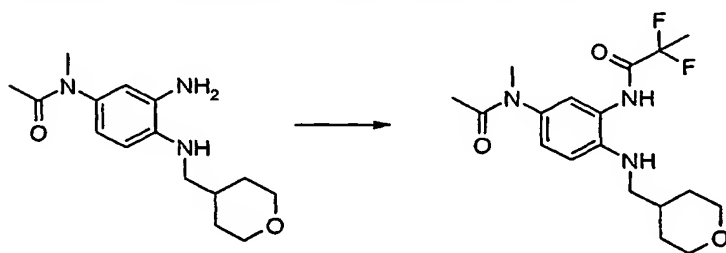
20

Step A. *N*-(4-([2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methylamino)sulfonyl)phenyl)-2-hydroxyacetamide



- 4*N* NaOH (10 drops) was added to a solution of 2-[(4-{[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino)sulfonyl}phenyl)amino]-2-oxoethyl acetate (74 mg, 0.13 mmol) (for preparation, see Steps B to G) in MeOH (5 mL). The reaction mixture was stirred for 1 hr. at room temperature and poured in water (100 mL). The mixture was acidified with concentrated HCl and the compound was extracted with EtOAc (3X). The combined organic layers were dried over anhydrous Na₂SO₄. The solvent was concentrated. The crude product was purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and then lyophilized to give the title compound as the corresponding TFA salt. Yield: 48 mg (57%); ¹H NMR (400 MHz, CDCl₃): δ 1.44 - 1.58 (m, 4 H), 2.25 (t, *J*=19.23 Hz, 4 H), 3.21 (s, 3 H), 3.29 - 3.44 (m, 2 H), 4.01 (d, *J*=11.33 Hz, 2 H), 4.24 (s, 2 H), 4.28 (d, *J*=7.42 Hz, 2 H), 7.30 (s, 1 H), 7.36 - 7.52 (m, 4 H), 7.66 (d, *J*=8.79 Hz, 2 H), 8.75 (s, 1 H); MS (ESI) (*M*+*H*)⁺: 523.0; Anal. Calcd. for C₂₄H₂₈F₂N₄O₅S + 0.90 TFA + 0.40 H₂O + 0.10 MeCN: C, 49.06; H, 4.75; N, 9.02. Found: C, 49.07; H, 4.76; N, 9.04.

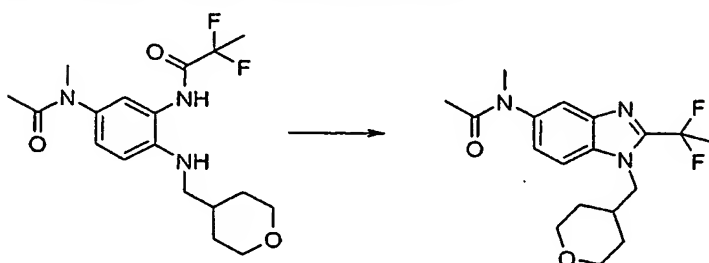
Step B. *N*-{5-[acetyl(methyl)amino]-2-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-2,2-difluoropropanamide



- HATU (1.44 g, 3.78 mmol) and *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide (1.00 g, 3.60 mmol) (for preparation, see Example 67) were added to a solution of 2,2-difluoropropanoic acid (0.40 g, 3.60 mmol) and DIPEA (0.75 mL, 4.32 mmol) in DMF (100 mL) at room temperature. The

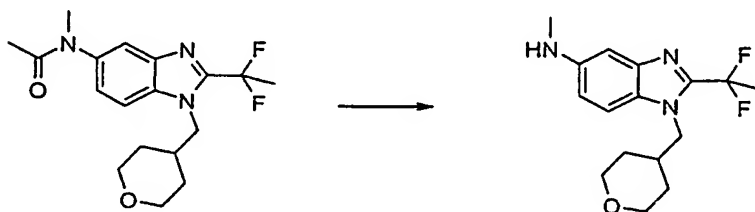
reaction mixture was stirred overnight. The solvent was concentrated and the crude product was recovered in EtOAc. The organic was washed with water, saturated NaHCO₃ solution and brine. The organic layer was dried over anhydrous Na₂SO₄ and filtered. The solvent was concentrated giving the title compound that was used for the next step without further purification. Yield: 1.00 g (75%); MS (ESI) (M+H)⁺: 370.2.

Step C. *N*-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide



N-{5-[acetyl(methyl)amino]-2-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-2,2-difluoropropanamide (1.00 g, 2.70 mmol) was heated to 90°C overnight in acetic acid (20 mL). The solvent was concentrated. The crude product was purified by flash chromatography on silica gel, using MeOH 3.5% and acetone 8% in DCM as eluent, giving the title compound. Yield: 0.48 g (50%); MS (ESI) (M+H)⁺: 352.0.

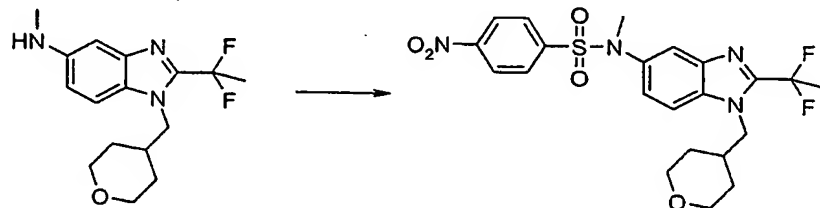
Step D. 2-(1,1-difluoroethyl)-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine



N-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide (0.48 g, 1.37 mmol) was heated to 80°C overnight in concentrated HCl (80 mL). The reaction mixture was cool to 0°C and brought to slightly basic pH using NaOH solution. The compound was extracted with EtOAc (3X) and the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and

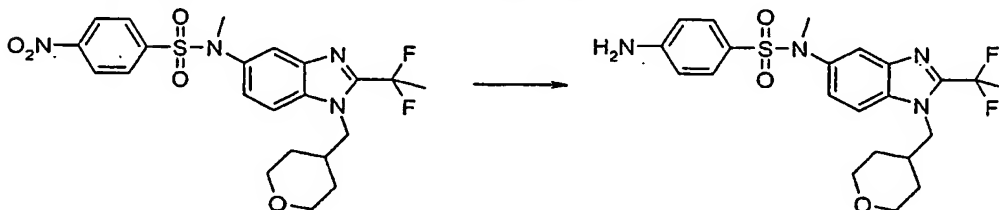
filtered. The solvent was concentrated giving the title compound that was used for the next step without further purification. Yield: 0.42 g (98%); MS (ESI) (M+H)⁺: 310.2.

Step E. *N*-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-nitrobenzenesulfonamide



4-Nitrobenzenesulfonyl chloride (0.28 g, 1.27 mmol) was added to a solution of 2-(1,1-difluoroethyl)-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (0.26 g, 0.84 mmol) and DMAP (0.21 g, 1.69 mmol) in DCE (50 mL). The reaction mixture was heated to 70°C for 1 hr. The solvent was concentrated. The crude product was purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and then lyophilized to give the title compound. Yield: 415 mg (99%); MS (ESI) (M+H)⁺: 495.3.

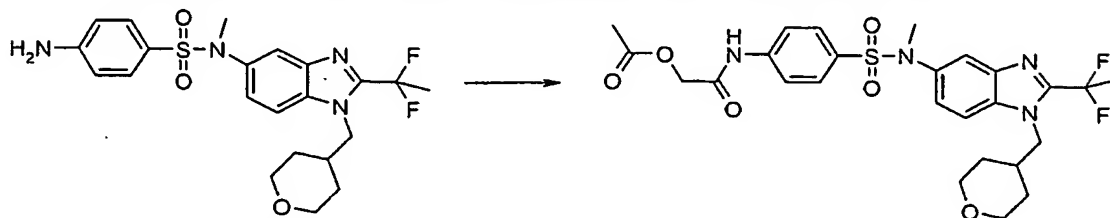
Step F. 4-amino-*N*-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



N-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-nitrobenzenesulfonamide (415 mg, 0.84 mmol) was hydrogenated in EtOAc (100 mL) catalyzed by 10% Pd/C at 40 psi H₂ in Parr shaker overnight at room temperature. The mixture was filtered over a celite pad. The solvent was concentrated giving the title compound that was used for the next step without further purification. Yield: 386 g (99%); MS (ESI) (M+H)⁺: 465.5.

25

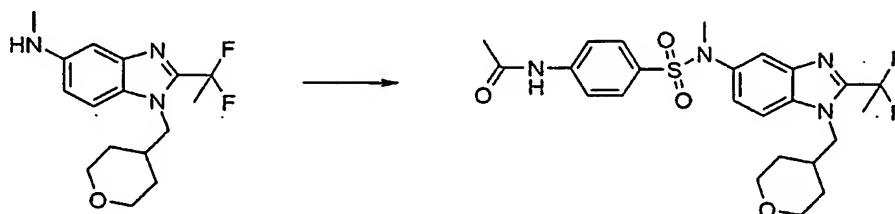
Step G. 2-[(4-[[[2-(1,1-difluoroethyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)amino]-2-oxoethyl acetate



2-Chloro-2-oxoethyl acetate (36 mg, 0.26 mmol) was added to a solution of
 5 4-amino-*N*-[2-(1,1-difluoroethyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (100 mg, 0.21 mmol) and Et₃N (44 μL, 0.32 mmol) in DCM (20 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 4 hrs. The solvent was concentrated. The crude product was purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O
 10 as eluent and then lyophilized to give the title compound. Yield: 74 mg (62%); MS (ESI) (M+H)⁺: 565.6.

Example 134

***N*-(4-[[[2-(1,1-difluoroethyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide**

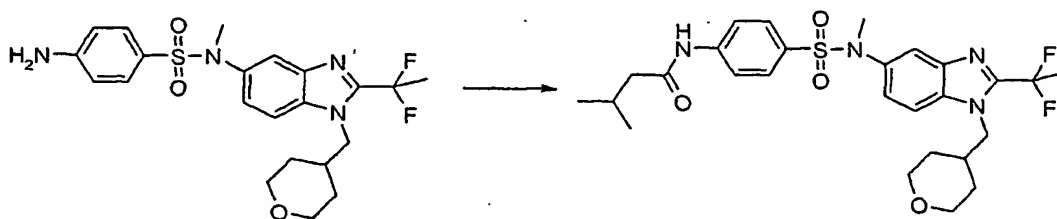


4-(Acetylamino)benzenesulfonyl chloride (45 mg, 0.19 mmol) was added to a solution of 2-(1,1-difluoroethyl)-*N*-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (50 mg, 0.16 mmol) (for preparation, see Example 133, Steps
 20 B to D) and DMAP (39 mg, 0.32 mmol) in MeCN (5 mL) at 70°C. The reaction mixture was stirred for 1 hr. and allowed to cool to room temperature. The solvent was concentrated. The crude product was purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and then lyophilized to give the title compound as the corresponding TFA salt. Yield: 87 mg (86%); ¹H NMR (400 MHz, CD₃OD): δ

1.39 - 1.55 (m, 5 H), 2.14 (s, 3 H), 2.21 (t, J=19.33 Hz, 3 H), 3.24 (s, 3 H) 3.32 - 3.38 (m, 2 H), 3.88 - 3.97 (m, 2 H), 4.34 (d, J=7.62 Hz, 2 H), 7.23 (dd, J=8.88, 2.05 Hz, 1 H), 7.35 (d, J=1.95 Hz, 1 H), 7.43 - 7.48 (m, 2 H), 7.64 (d, J=8.79 Hz, 1 H), 7.67 - 7.73 (m, 2 H); MS (ESI) (M+H)⁺: 507.0; Anal. Calcd. for C₂₄H₂₈F₂N₄O₄S + 1.20 TFA + 0.20 H₂O + 0.10 MeCN: C, 49.07; H, 4.63; N, 8.82. Found: C, 49.04; H, 4.59; N, 8.84.

Example 135

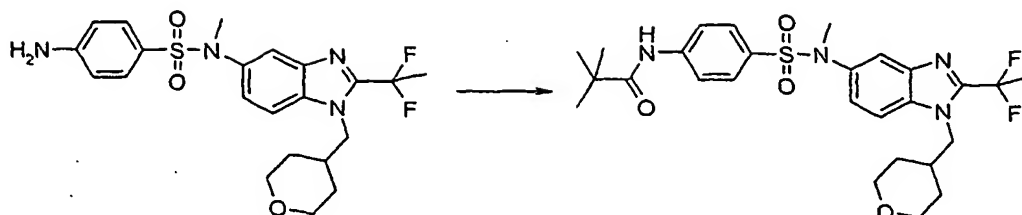
N-(4-[[[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-3-methylbutanamide



3-Methylbutanoyl chloride (15 mg, 0.12 mmol) was added to a solution of 4-amino-*N*-[[[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (50 mg, 0.10 mmol) (for preparation, see Example 133, Steps B to F) and Et₃N (22 µL, 0.16 mmol) in DCM (10 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was concentrated. The crude product was purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and then lyophilized to give the title compound as the corresponding TFA salt. Yield: 25 mg (35%); ¹H NMR (400 MHz, CDCl₃): δ 1.03 (d, J=6.44 Hz, 6 H), 1.43 - 1.56 (m, 4 H), 2.16 - 2.35 (m, 6 H), 3.13 (s, 1 H), 3.21 (s, 3 H), 3.29 - 3.41 (m, 2 H), 3.94 - 4.05 (m, 2 H), 4.27 (d, J=7.42 Hz, 2 H), 7.33 (s, 1 H), 7.37 - 7.43 (m, 2 H), 7.45 - 7.53 (m, 3 H), 7.63 (d, J=8.79 Hz, 2 H); MS (ESI) (M+H)⁺: 549.0; Anal. Calcd. for C₂₇H₃₄F₂N₄O₄S + 1.40 TFA + 0.30 MeCN: C, 50.67; H, 5.08; N, 8.36. Found: C, 50.68; H, 5.07; N, 8.32.

Example 136

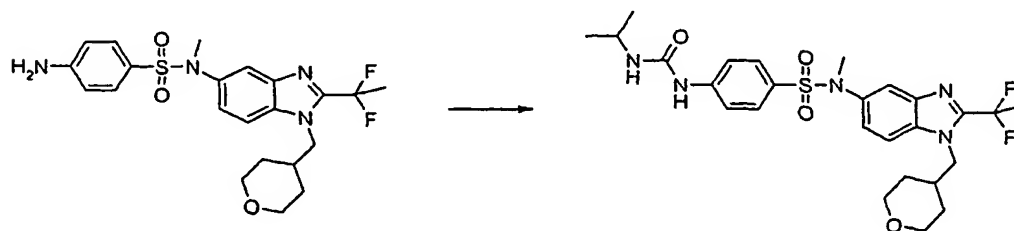
N-(4-[[[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2,2-dimethylpropanamide



2,2-Dimethylpropanoyl chloride (15 mg, 0.12 mmol) was added to a solution of 4-amino-N-[2-(1,1-difluoroethyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylbenzenesulfonamide (50 mg, 0.10 mmol) (for preparation, see Example 133, Steps B to F) and Et₃N (22 μ L, 0.16 mmol) in DCM (10 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was concentrated. The crude product was purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and then lyophilized to give the title compound. Yield: 31 mg (43%); ¹H NMR (400 MHz, CDCl₃): δ 1.34 (s, 9 H), 1.46 - 1.56 (m, 3 H), 1.69 (s, 2 H), 2.17 (s, 3 H), 2.26 (t, J=19.23 Hz, 3 H), 3.29 - 3.40 (m, 2 H), 3.98 (dt, J=11.23, 2.98 Hz, 2 H), 4.26 (d, J=7.42 Hz, 2 H), 5.30 (s, 1 H), 7.31 (s, 1 H), 7.32 - 7.42 (m, 2 H), 7.47 - 7.53 (m, 1 H), 7.59 (s, 1 H), 7.62 - 7.69 (m, 2 H); MS (ESI) (M+H)⁺: 549.0; Anal. Calcd. for C₂₇H₃₄F₂N₄O₄S: C, 59.11; H, 6.25; N, 10.21. Found: C, 59.54; H, 6.16; N, 10.05.

Example 137

N-[2-(1,1-difluoroethyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-4-[[isopropylamino]carbonyl]amino-N-methylbenzenesulfonamide

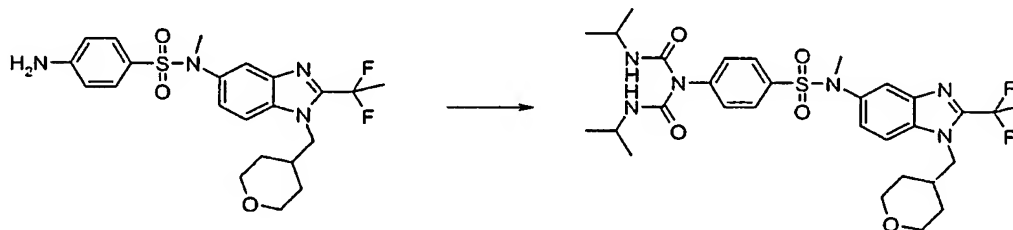


2-Isocyanatopropane (excess) was added to a solution of 4-amino-N-[2-(1,1-difluoroethyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylbenzenesulfonamide (50 mg, 0.10 mmol) (for preparation, see Example 133, Steps B to F) in DCE (5 mL). The reaction mixture was stirred at 90°C overnight. The

solvent was concentrated. The crude product was purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and then lyophilized to give the title compound as the corresponding TFA salt. Yield: 12 mg (16%); ¹H NMR (400 MHz, CDCl₃): δ 1.20 (d, J=6.44 Hz, 6 H), 1.23 (d, J=6.64 Hz, 1 H), 1.44 - 1.57 (m, 4 H), 1.80 (s, 1 H), 2.26 (t, J=19.14 Hz, 3 H), 3.19 (s, 3 H), 3.28 - 3.41 (m, 2 H), 3.91 - 4.05 (m, 3 H), 4.27 (d, J=7.42 Hz, 2 H), 7.22 (s, 1 H), 7.31 - 7.48 (m, 6 H); MS (ESI) (M+H)⁺: 550.0.

Example 138

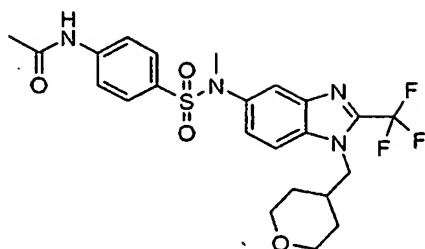
10 4-{Bis[(isopropylamino)carbonyl]amino}-N-[2-(1,1-difluoroethyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylbenzenesulfonamide



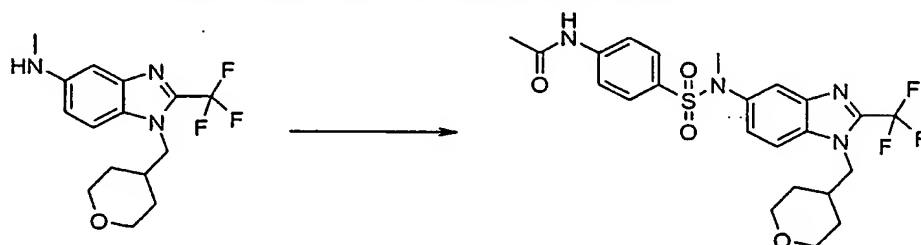
The title compound was obtained as a by-product in Example 137. The material was purified by preparative reverse-phase HPLC using 10-90% CH₃CN/H₂O as eluent and then lyophilized to give the corresponding TFA salt. Yield: 18 mg (22%); ¹H NMR (400 MHz, CDCl₃): δ 1.15 (d, J=6.64 Hz, 12 H), 1.44 - 1.55 (m, 4 H), 1.82 (s, 2 H), 2.27 (t, J=19.23 Hz, 3 H), 3.28 (s, 3 H), 3.29 - 3.39 (m, 2 H), 3.88 - 4.03 (m, 3 H), 4.25 (d, J=7.42 Hz, 2 H), 6.55 (s, 1 H), 7.24 (dd, J=8.79, 1.95 Hz, 1 H), 7.39 (d, J=8.59 Hz, 2 H), 7.53 (d, J=1.76 Hz, 1 H), 7.73 (d, J=8.59 Hz, 2 H); MS (ESI) (M+H)⁺: 635.0.

Example 139

25 N-[4-({methyl[1-(tetrahydro-2H-pyran-4-ylmethyl)-2-(trifluoromethyl)-1H-benzimidazol-5-yl]amino}sulfonyl)phenyl]acetamide

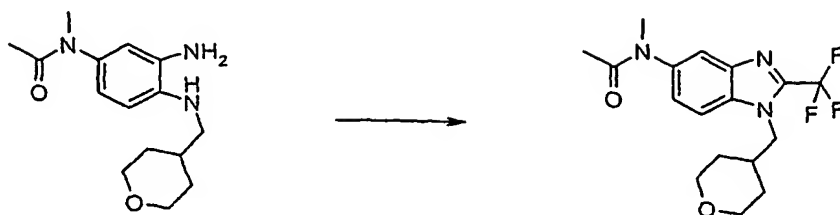


Step A. *N*-[4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]acetamide



- 5 *N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-amine hydrochloride (76.1 mg, 0.2 mmol) (for preparation, see following Steps B and C), DMAP (97.7 mg, 0.8 mmol) and 4-(acetaminophenyl)sulfonyl chloride (93.5 mg, 0.4 mmol) in MeCN (5 mL) were stirred overnight at room temperature. The reaction mixture was quenched with H₂O (6 mL). Upon evaporation, the crude
- 10 product was purified by reversed-phase HPLC using 20-70% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 49.1 mg (48%). ¹HNMR (400 MHz, CD₃OD): 1.39 - 1.56 (m, 4 H), 2.14 (s, 3 H), 2.19 - 2.32 (m, 1 H), 3.24 (s, 3 H), 3.31 - 3.39 (m, 2 H), 3.85 - 4.01 (m, 2 H), 4.32 (d, *J*=7.42 Hz, 2 H), 7.32 (dd, *J*=8.88, 2.05 Hz, 1 H), 7.40 (d, *J*=1.95 Hz, 1 H), 7.43 - 7.49 (m, 2
- 15 H), 7.67 - 7.75 (m, 3 H). MS (ESI) (*M*+*H*)⁺ = 511.0. Anal. Calcd for C₂₃H₂₅F₃N₄O₄S + 0.4 TFA + 0.2 H₂O (559.75): C, 51.07, H, 4.65, N, 10.01; Found: C, 51.16; H, 4.74; N, 9.65.

- 20 **Step B. *N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]acetamide**



A solution of *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide hydrochloride (395.1 mg, 1.42 mmol) (for preparation see Example 67) in trifluoroacetic acid (10 mL) was heated to reflux for 20 h. After evaporation of the solvent, the crude product was used directly for next step without purification. MS (ESI) (M+H)⁺: 356.02.

Step C. *N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-amine



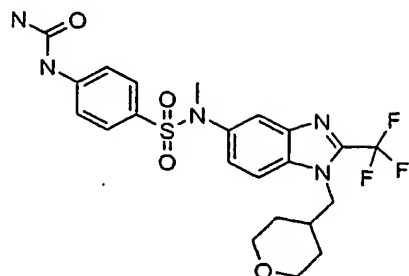
10

The crude *N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]acetamide (~500 mg, 1.42 mmol) was dissolved in 10 mL of EtOH-2*N* HCl (3:2), and then heated at 120°C in a Personal Chemistry SmithSynthesizer microwave instrument for 4 h. After concentration and dried *in vacuo*, 539 mg (100%) of a grey white solid was obtained as the title product, which was used directly for Step A. MS (ESI) (M+H)⁺ = 314.20.

Example 140

4-[(aminocarbonyl)amino]-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide

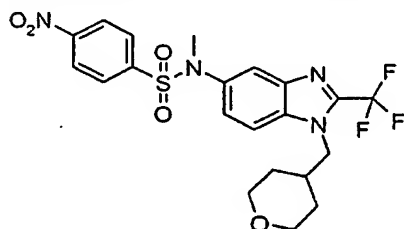
20



Following the procedure for Step A in Example 139, using *N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-amine hydrochloride (76.1 mg, 0.2 mmol) (for preparation, see the steps B and C in Example 139), DMAP (97.7 mg, 0.8 mmol) and 4-[(aminocarbonyl)amino]benzenesulfonyl chloride (94.0 mg, 0.4 mmol) in MeCN (6 mL), the crude product was purified by reversed-phase HPLC using 20-50% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 42.9 mg (42%). ¹HNMR (400 MHz, CD₃OD): δ 1.40 - 1.52 (m, 4 H), 2.15 - 2.34 (m, 1 H), 3.23 (s, 3 H), 3.31 - 3.40 (m, 2 H), 3.87 - 3.98 (m, 2 H), 4.32 (d, J=7.81 Hz, 2 H), 7.32 (dd, J=8.88, 2.05 Hz, 1 H), 7.37 - 7.43 (m, 3 H), 7.48 - 7.56 (m, 2 H), 7.72 (d, J=8.79 Hz, 1 H). MS (ESI) (M+H)⁺ = 512.0. Anal. Calcd for C₂₂H₂₄F₃N₅O₄S + 0.3 TFA (545.73): C, 49.74, H, 4.49, N, 12.83; Found: C, 49.84; H, 4.55; N, 12.78.

15 Example 141

N-methyl-4-nitro-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide

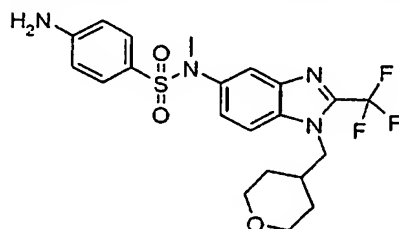


Following the procedure for Step A in Example 139, using *N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-amine hydrochloride (387.0 mg, 1.0 mmol) (for preparation, see the steps B and C in Example 139), DMAP (488.7 mg, 4.0 mmol) and 4-nitrobenzenesulfonyl chloride (443.2 mg, 2.0 mmol) in MeCN (10 mL), the crude product was purified by MPLC using

Hex/EtOAc (1:1) on silica gel to give 295.0 mg (59%) of a yellow solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 1.39 - 1.54 (m, 4 H), 2.14 - 2.34 (m, 1 H), 3.32 (s, 3 H), 3.33 - 3.40 (m, 2 H), 3.86 - 4.01 (m, 2 H), 4.32 (d, J=7.42 Hz, 2 H), 7.31 (dd, J=8.88, 2.05 Hz, 1 H), 7.45 (d, J=2.15 Hz, 1 H), 7.74 (d, J=8.98 Hz, 1 H), 7.76 - 7.82 (m, 2 H), 8.27 - 8.42 (m, 2 H). MS (ESI) (M+H)⁺ = 499.0. Anal. Calcd for C₂₁H₂₁F₃N₄O₅S+ 0.50 TFA+0.20 H₂O (559.10): C, 47.26; H, 3.95; N, 10.02; Found: C, 47.24; H, 3.80; N, 10.20.

Example 142

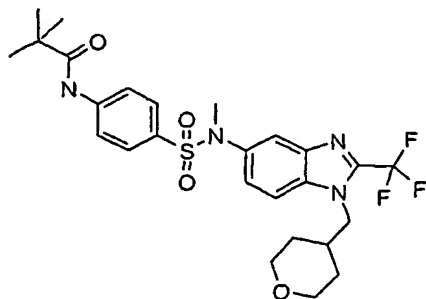
10 4-amino-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



N-methyl-4-nitro-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (235.6 mg, 0.47 mmol) (for preparation, see the Example 141) was hydrogenated in ethyl acetate (20 mL) catalyzed by 10% Pd/C (90 mg) at 30-40 psi H₂ in Parr shaker for 5 h at room temperature. After filtration through celite and concentration, 229.8 mg (100%) of a white solid was obtained. Small amounts of the crude product was purified by reversed-phase HPLC using 20-70% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. ¹HNMR (400 MHz, CD₃OD): δ 1.38 - 1.55 (m, 4 H), 2.15 - 2.35 (m, 1 H), 3.18 (s, 3 H), 3.33 - 3.40 (m, 2 H), 3.82 - 4.02 (m, 2 H), 4.32 (d, J=7.62 Hz, 2 H), 6.58 - 6.69 (m, 2 H), 7.15 - 7.23 (m, 2 H), 7.35 (dd, J=8.98, 1.95 Hz, 1 H), 7.40 (d, J=1.56 Hz, 1 H), 7.71 (d, J=8.79 Hz, 1 H). MS (ESI) (M+H)⁺ = 469.0. Anal. Calcd for C₂₁H₂₃F₃N₄O₃S+ 0.40 TFA (514.11): C, 50.93; H, 4.59; N, 10.90; Found: C, 51.00; H, 4.72; N, 10.54.

Example 143

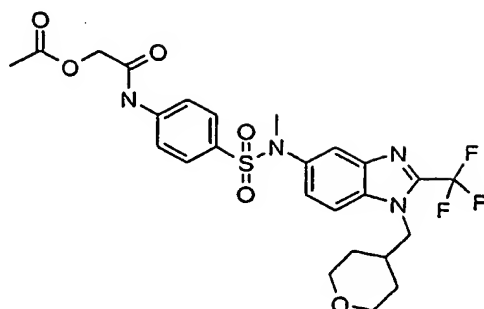
2,2-dimethyl-*N*-[4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]propanamide



4-Amino-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (50.3 mg, 0.107 mmol) (for preparation, see the Example 142), DMAP (59.0 mg, 0.483 mmol) and trimethylacetyl chloride (14.7 mg, 0.122 mmol) in MeCN (5 mL) were stirred for 6 h at room temperature. The reaction mixture was diluted with EtOAc (100 mL), washed with saturated NaHCO₃ (10 mL) and saturated NaCl (10 mL), and dried over Na₂SO₄. Upon evaporation, the residue was purified by by MPLC using Hex/EtOAc (1:1) on silica gel to give 30.5 mg (52%) of a white solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 1.29 (s, 9 H), 1.39 - 1.58 (m, 4 H), 2.15 - 2.37 (m, 1 H), 3.24 (s, 3 H), 3.31 - 3.40 (m, 2 H), 3.87 - 3.99 (m, 2 H), 4.32 (d, J=7.62 Hz, 2 H), 7.32 (dd, J=8.88, 2.05 Hz, 1 H), 7.40 (d, J=1.95 Hz, 1 H), 7.42 - 7.49 (m, 2 H), 7.72 (d, J=8.98 Hz, 1 H), 7.74 - 7.79 (m, 2 H), 9.35 (s, 1 H). MS (ESI) (M+H)⁺ = 553.0. Anal. Calcd for C₂₆H₃₁F₃N₄O₄S+ 0.1 TFA+0.50 H₂O (573.03): C, 54.92; H, 5.65; N, 9.78; Found: C, 54.77; H, 5.54; N, 10.09.

Example 144

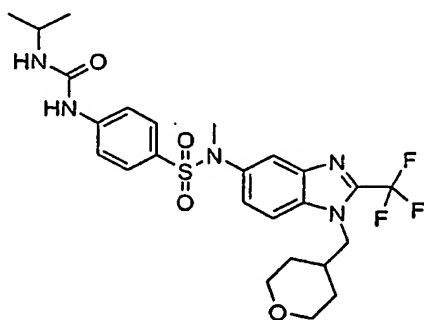
2-{{[4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]amino}-2-oxoethyl acetate



Following the procedure for Example 143, using 4-Amino-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (113.0 mg, 0.241 mmol) (for preparation, see the Example 5 142), DMAP (109.0 mg, 0.892 mmol) and 2-chloro-2-oxoethyl acetate chloride (38.1 mg, 0.279 mmol) in MeCN (10 mL), the crude product was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 90.0 mg (66%) of a white solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 1.41 - 1.54 (m, 4 H), 2.16 (s, 3 H), 2.20 - 2.33 (m, 1 H), 3.25 (s, 3 H), 3.31 - 3.40 (m, 2 H), 3.87 - 3.98 (m, 2 H), 4.32 (d, 10 J=7.62 Hz, 2 H), 4.69 (s, 2 H), 7.32 (dd, J=8.88, 2.05 Hz, 1 H), 7.41 (d, J=1.56 Hz, 1 H), 7.44 - 7.50 (m, 2 H), 7.69 - 7.76 (m, 3 H), 10.24 (s, 1 H). MS (ESI) (M+H)⁺ = 569.1. Anal. Calcd for C₂₅H₂₇F₃N₄O₆S + 0.1 TFA + 0.40 H₂O (587.18): C, 51.55; H, 4.79; N, 9.54; Found: C, 51.60; H, 4.74; N, 9.56.

15 Example 145

4-[(isopropylamino)carbonyl]amino}-N-methyl-N-[1-(tetrahydro-2H-pyran-4-ylmethyl)-2-(trifluoromethyl)-1H-benzimidazol-5-yl]benzenesulfonamide

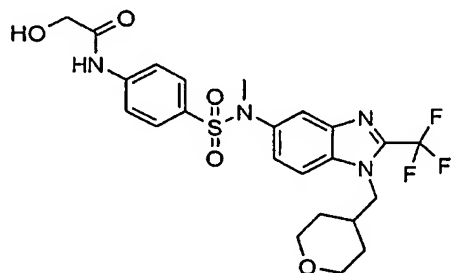


20 4-Amino-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (31.3 mg, 0.067 mmol) (for preparation, see

the Example 142) and 2-isocyanatopropane (0.5 mL) in DCE (5 mL) was heated overnight at 80 °C. After evaporation, the crude product was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 17.2 mg (46%) of a white solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 1.17 (d, J=6.44 Hz, 6 H), 1.41 - 1.53 (m, 4 H), 2.18 - 2.33 (m, 1 H), 3.23 (s, 3 H), 3.31 - 3.39 (m, 2 H), 3.83 - 3.90 (m, 1 H), 3.90 - 3.96 (m, 2 H), 4.32 (d, J=7.42 Hz, 2 H), 7.32 (dd, J=8.88, 2.05 Hz, 1 H), 7.36 - 7.40 (m, 2 H), 7.40 (d, J=1.56 Hz, 1 H), 7.46 - 7.52 (m, 2 H), 7.72 (d, J=8.59 Hz, 1 H). MS (ESI) (M+H)⁺ = 554.0. Anal. Calcd for C₂₅H₃₀F₃N₅O₄S+ 0.70 TFA+0.20 H₂O +0.5CH₃OH (653.06): C, 49.48; H, 5.11; N, 10.72; Found: C, 49.50; H, 5.16; N, 10.71.

Example 146

2-Hydroxy-N-[4-({methyl[1-(tetrahydro-2H-pyran-4-ylmethyl)-2-(trifluoromethyl)-1H-benzimidazol-5-yl]amino}sulfonyl)phenyl]acetamide



2-{{[4-({Methyl[1-(tetrahydro-2H-pyran-4-ylmethyl)-2-(trifluoromethyl)-1H-benzimidazol-5-yl]amino}sulfonyl]phenyl]amino}-2-oxoethyl acetate (56.3 mg, 0.107 mmol) (for preparation, see the Example 144) and a drop of sodium methoxide (25% in MeOH) in MeOH (10 mL) was stirred overnight at room temperature. After evaporation, the crude product was purified by reversed-phase HPLC using 15-65% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 36.6 mg (65%). ¹HNMR (400 MHz, CD₃OD): δ 1.39 - 1.56 (m, 4 H), 2.15 - 2.35 (m, 1 H), 3.25 (s, 3 H), 3.32 - 3.41 (m, 2 H), 3.86 - 4.00 (m, 2 H), 4.13 (s, 2 H), 4.32 (d, J=7.62 Hz, 2 H), 7.33 (dd, J=8.88, 2.05 Hz, 1 H), 7.41 (d, J=1.56 Hz, 1 H), 7.45 - 7.53 (m, 2 H), 7.72 (d, J=8.40 Hz, 1 H), 7.76 - 7.85 (m, 2 H). MS (ESI) (M+H)⁺ = 527.0. Anal. Calcd for C₂₃H₂₅F₃N₄O₅S+0.80 H₂O (540.95): C, 51.07; H, 4.96; N, 10.36; Found: C, 51.22; H, 5.11; N, 10.14.

